Gold(I)-catalysed Synthesis of Cyclic Sulfamidates by Intramolecular Allene Hydroamination

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1. Abstract

The work reported in this thesis outlines the gold(I)-catalysed synthesis of cyclic sulfamidates by intramolecular allene hydroamination. Work carried out in an attempt to prepare a novel acyl anion equivalent is also included but endeavours were halted after one year of study. The thesis is divided into six chapters**:**

Chapter one provides an introduction to the reactivity of gold, current metal-catalysed hydroamination reactions and allene structure, synthesis and reactivity. The current synthetic methods for the preparation of sulfamidates and their uses is also covered.

Chapter two outlines the attempted use of the Burgess reagent to prepare olefinically substituted sulfamidates and the attempts to reverse regioselectivity in sulfamidate synthesis.

Chapter three includes an initial proof of concept in gold(I) catalysis and an account of substrate synthesis. Allenes were synthesised by Crabbé homologation or Johnson-Claisen rearrangement reactions. The allenes were then converted to the corresponding sulfamates.

Chapter four outlines our studies of gold(I)-catalysed hydroamination. This includes optimisation of catalyst and the effects of substitution on reaction rate and stereochemical hypothesis. The current scope and limitations of this chemistry is also discussed.

Chapter five outlines the research work attempted within the first year of study. The work focussed on the attempted preparation of a thermally unmasked acyl anion equivalent.

Chapter six provides a formal report of the experimental procedures.

Stereochemical abstract: All compounds with stereogenic centres were prepared as racemic mixtures but only one enantiomer is represented in the schemes.

2. Acknowledgements

Firstly, I would like to express my sincere gratitude to Dr Magnus Bebbington for providing me with the opportunity to work under his supervision. I will be eternally grateful for his relentless patience, guidance and encouragement during my studies.

Thanks to everyone who has passed through the doors of the Bebbington Lab, especially Robert for his friendship and strong opinions.

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I would like to thank Toria for her unfaltering friendship through the years and for listening to me harp on about organic chemistry and feining interest accordingly.

To my parents, I owe a lot, and appreciate your enthusiasm and support during my studies.

Finally, I must thank Gary for being my lighthouse in stormy seas. Maybe now we can finally set a date…

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3. Contents

4. Abbreviations

δ	NMR chemical shift
ν	wavenumber
Å	Angstrøm
Ac	acetyl
aq.	aqueous
atm.	atmosphere
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
b.p.	boiling point
br.	broad
cat.	catalyst
cm^{-1}	wavenumbers
d	doublet
DCM	dichloromethane
d.e.	diastereomeric excess
°C	degrees Celsius
DEPT	distortionless enhancement by polarisation transfer
DMA	dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	*N*,*N* dimethylformamide
DMSO	dimethylsulfoxide
E	electrophile
ee	enantiomeric excess
eq.	equivalents

ESI	electrospray ionisation
eV	electronvolt
FTIR	Fourier transform infra-red
GC	gas chromatography
lit.	literature
HRMS	high resolution mass spectrometry
IR	infra-red
J	NMR coupling constant
LDA	lithium diisopropylamide
M	molar (mol/litre)
m	multiplet
Mbs	*p*-methoxybenzenesulfonyl
m-CPBA	*meta*-chloroperoxybenzoic acid
MHz	mega Hertz
min(s)	minute(s)
m.p.	melting point
MS	molecular sieves
m/z	mass/charge ratio
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
Nu	nucleophile
o/n	overnight
OTf	trifluoromethanesulfonate
p	*para*
PCC	pyridiniumchlorochromate
Pd/C	palladium on activated charcoal

ppm	parts per million
Pr	propyl
quin.	quintet
R_f	retention factor
RT	room temperature
s	singlet
sat.	saturated
SM	starting material
t	triplet
t	*tertiary*
Ts	*para*-toluene sulfonate (Tosyl)
TBAF	tetrabutylammonium fluoride
temp.	temperature
THF	tetrahydrofuran
TLC	thin layer chromatography
TMDS	tetramethyldisilazane
TMS	tetramethylsilane
TOF	turn over frequency
TON	turn over number
Z	atomic number

Chapter 1

Introduction

Chapter One: Introduction

This thesis will focus on gold(I)-catalysed hydroamination of allenes in the preparation of cyclic sulfamidates. This introductory chapter will cover the topics of gold catalysis, hydroamination, preparation and reactivity of allenes and sulfamidate chemistry.

1.1 Gold - the element

Gold has been a valuable and highly sought-after metal to mankind from the very early days.[1] The precious metal has always been held in high regard as shown by King Midas in Greek mythology. Most of the gold found on earth is located in the core and it is believed that the high density of the metal led to it sinking there. Most gold that is mined today is believed to come from later meteorite deposits.[2]

Besides its widespread monetary and symbolic functions, gold has many practical uses. Gold has applications in medicine due to its high biocompatibility in the metallic form. Gold is used in dentistry, the treatment of arthritis and recently has been of interest in cancer research.[3]

Its high malleability, ductility, resistance to corrosion and most other chemical reactions and conductivity of electricity led to many uses of gold including electric wiring, coloured-glass production and gold leafing.[4]

Although gold is the most inert of the noble metals, it still forms many diverse compounds. The oxidation state of gold in its compounds ranges from -1 to +5, but gold(I) and gold (III) dominate its chemistry.[5] Gold(I), referred to as the aurous ion, is the most common oxidation state. With soft ligands such as thioethers, thiolates and tertiary phosphines, gold(I) complexes have typically linear geometry at the metal.[6]

While the stoichiometric chemistry of gold has intensively and continuously been investigated, this close relationship between gold and chemical applications was lost during the development of metal-catalysed reactions. It is likely a low catalytic activity was mistakenly deduced from the inertness of elemental gold that only dissolves in *aqua regia* or oxidants such as air, the latter only in the presence of strong ligands such as cyanide.[7] It is also likely that gold has been overlooked as a suitable catalyst as many may perceive it as costly. However, gold is often less expensive than other metals used in large-scale processes such as rhodium, palladium and platinum.[4] Gold is often recycled from stoichiometric reactions unlike platinum and with thousands of tons produced through mining every year the price of gold is much more stable compared to other noble metals.[4] It must also be noted that often the cost of the ligand is responsible for elevated catalyst prices.

1.1.1 Reactivity of gold

The electronic structure of gold can provide an insight into its observed reactivity. The key factor influencing the characteristics of gold with regard to the electronic structure are the strong relativistic effects. Beyond the large Au-L bond strengths, further corroboration of this distortion from the otherwise expected electronic structure lies in the phenomenon of "aurophilicity",[8] the tendency for gold-gold interactions to be stabilising on the order of hydrogen bonds, and also in the large first ionisation potential observed for gold (9.22eV versus 7.57eV for Ag).

Unlike copper(I) and silver(I) complexes, which tend to adopt tricoordinate and tetracoordinate geometries[9] respectively, gold(I) adopts a linear bicoordinate geometry. It is usually necessary to abstract a ligand from neutral bicoordinate gold(I) species to induce catalytic reactivity. Compared to the corresponding copper complexes, organogold(I) complexes are not very nucleophilic and this is due to the 5d electrons being held more strongly than the 3d electrons due to decreased electron/electron repulsion in the diffuse 5d orbitals, resulting in a less electron-rich metal which is not susceptible to oxidative addition.[10]

Studies on reductive elimination from $LR_3Au(III)$ complexes shows that this is also disfavoured.[10] Gold(I) species are therefore quite tolerant of oxygen so often reactions can be run in the presence of air. However, there is limited scope for gold-catalysed transformations which tolerate the presence of water.[11]

With the increasing use of gold as a catalyst, there has been growing interest in gaining a deeper understanding of the fundamental properties of gold. Gold (Z = 79) has the atomic configuration [Xe]$4f^{14}5d^{10}6s^1$. Gold(I) is strongly Lewis acidic with respect to C-C π-systems, and this coupled with its ability to stabilise cationic reaction intermediates leads to catalysts with unique reactivity which can be exploited in gold catalysis. Relativistic effects are key in theoretically rationalising the observed reactivity.[12]

$$H\Psi = E\Psi$$

Figure 1: Schrödinger equation

The Schrödinger equation (Figure 1), from which all of our concepts in theoretical chemistry are derived is nonrelativistic in the sense that the possibility of velocity-dependent mass is not admitted. It assumes that the velocity of light is infinite. Einstein's Theory of relativity postulates that the mass m of a particle increases as its speed ν moves toward that of light c, according to

$$m = \frac{m_0}{(1 - \left(\frac{v}{c}\right))^{1/2}}$$

Figure 2: Relativistic mass

where m_0 is its rest mass. For atoms with an atomic number greater than ~50 (Sn), the 1*s* electrons are sufficiently influenced by the nuclear mass that their speed approaches that of light and their mass increases accordingly as outlined in Figure 2. The innermost *s* orbital therefore contracts, and the outer *s* shells shrink in sympathy; electrons in *p*-

orbitals are also affected to some extent, but those in *d* and *f* orbitals less so, because their probability of being close to the nucleus is low. The effective potentials of *d* and *f* electrons are, however, better screened because of the relative contractions of the *s* and *p* shells, and their orbitals, therefore increase in energy and expand radially. The so-called "relativistic contraction" of the 6*s* orbital becomes greater on moving across the Third Transition Series and is greatest for gold (Figure 3).

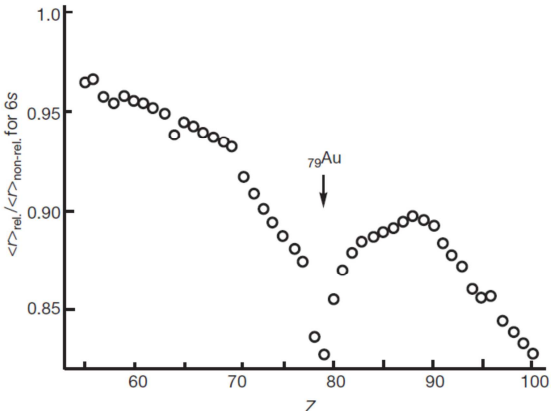


Figure 3: Calculated relativistic contraction of the 6s orbital

The colour of gold can also be explained by considering the relativistic effects of the metal. Excitation of the 5*d* electrons to the Fermi level occurs with a band gap of 2.38eV and this leads to the absorption of blue light. The band gap in silver is much larger, so absorption occurs in the UV region.

Cationic gold(I) species, with an empty 6*s* orbital, are superior Lewis acids compared with other group 11 metals for many transformations, and intuitively it seems that relativistic contraction of the valence *s* or *p* orbitals of gold should be responsible, because they should correspond to a relatively low-lying lowest unoccupied molecular orbital (LUMO) and therefore strong Lewis acidity.

Many developments in gold catalysis depend on the propensity of gold to activate C=C π-systems to nucleophilic addition. The bonding situation in transition-metal complexes with alkenes and alkynes as π ligands is usually discussed within the framework of the

Dewar-Chatt-Duncanson (DCD) model,[13] which considers the bond as a donor-acceptor interaction between two closed shell fragments. The DCD model assumes that a σ bond is formed by overlap of the π system of the ligand with an empty metal orbital of suitable symmetry. A π interaction then results through back-donation of electron density from a filled metal d-orbital into an antibonding π* orbital of the alkene or alkyne.[14]

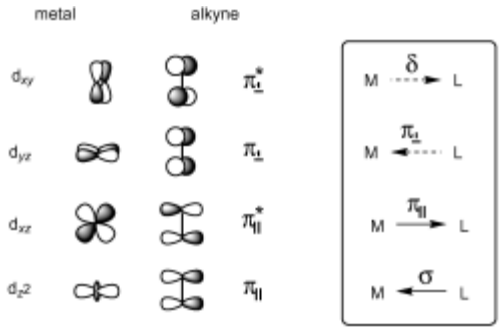
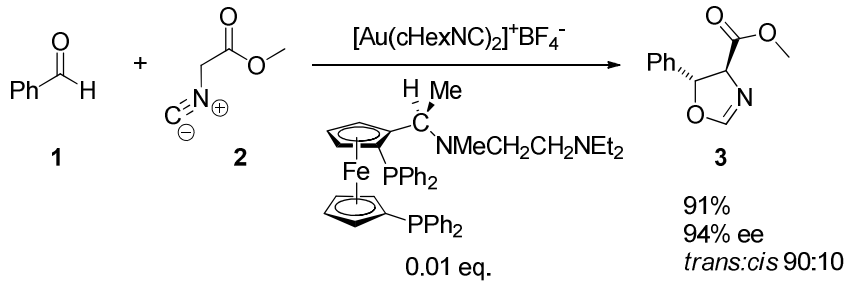


Figure 4: Metal-alkyne bonding orbitals

There are four principal components that can contribute to the bonding of alkynes as ligands (Figure 4). The in-plane $\pi_{\parallel}$ orbitals are responsible for a σ-symmetric M←L donation as well as for the π-symmetric M→L back-donation referred to above. The orthogonal, out–of-plane $\pi_{\perp}$ orbitals can engage in M←L donation referred to above. The orthogonal, out-of-plane $\pi_{\perp}$ orbitals can engage in M←L π donation (an interaction of importance in alkyne complexes in which the ligand serves as a four-electron donor), while mixing of an occupied d orbital of the metal and the empty $\pi_{\perp}^{*}$ orbital of the alkyne can result in an additional component of M→L back-donation. This latter interaction, however, has δ symmetry, which results in only a weak overlap, and therefore leads to a minute contribution to the bonding.

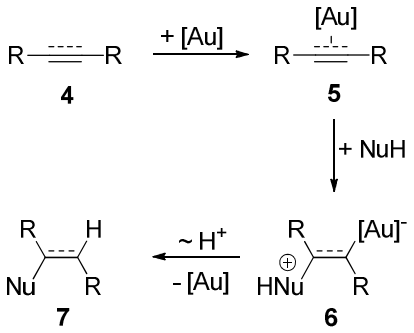
1.1.2 Gold catalysis

The first examples of gold catalysis were recorded in the 1980's. An early example was described by Ito in which benzaldehyde and methyl isocyanate were reacted with a chiral ferrocenylphosphine ligand and cationic gold(I) compound $(Au(cHexCN)_2)BF_4$ to form a chiral oxazoline (Scheme 1).[15]



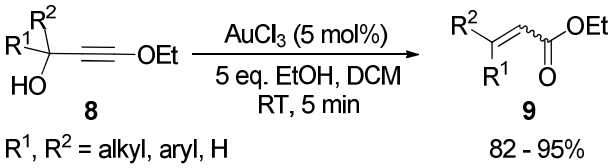
Scheme 1: An early example of gold catalysis

The most common use of gold in catalysis is nucleophilic addition to C-C multiple bonds.[16] Alkynes are the most popular substrates with olefins and allenes also having been investigated. The simplest example is shown in Scheme 2 where gold interacts with the π-system of substrate **4** to afford the intermediate **5**. Isotopic labelling experiments show that nucleophilic attack normally occurs *anti* to gold to give a vinylgold species **6**.[16] Protodemetallation liberates the gold species and affords product **7**.



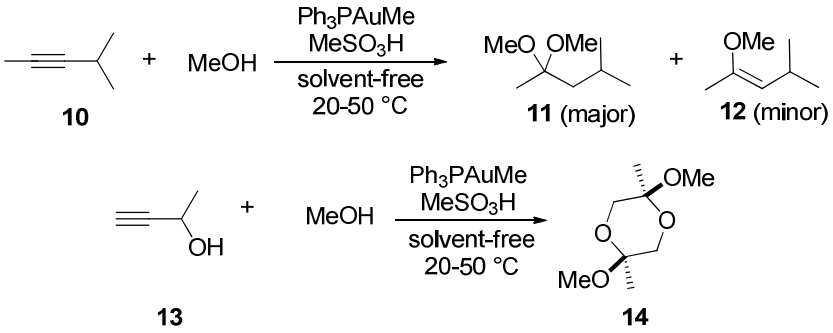
Scheme 2: Gold activation of alkynes to nucleophilic attack

The preparation of α,β-unsaturated esters from alkoxy-alkynes was reported by Dudley *et al. via* a $AuCl_3$-catalysed Meyer-Schuster type rearrangement (Scheme 3).[17] It is interesting to note that propargylic alcohols did not react with Utimoto's catalysts. These substrates would be difficult to prepare by the Horner-Wadsworth-Emmons olefination as it would not tolerate bulky R_1 and R_2 substituents. It should be noted that the *E/Z* selectivity was poor for these reactions.



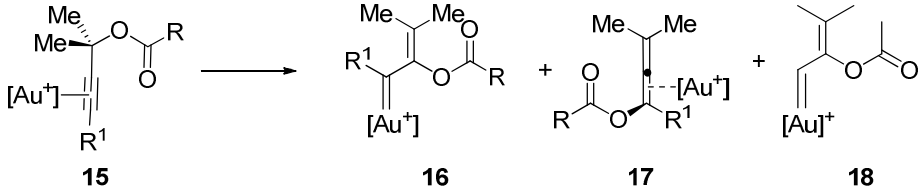
Scheme 3: Meyer-Schuster rearrangement to give α,β-unsaturated esters

Major advances were made when Teles introduced cationic gold(I)-phosphane complexes as catalysts for the addition of alcohols to alkynes (Scheme 4).[18] Teles was the first to use acidic promoters for the *in situ* generation of the catalyst. This type of homogenous catalyst, especially the $Ph_3PAu^+X^-$ system, is still the most commonly used system for these transformations. It was found to have very high activity (TON up to 10^5 and TOF up to $5400h^{-1}$). In Scheme 4 methanol attacks the alkyne **10** at the sterically less hindered position and forms the enol ether **12** in very small amounts as a by-product. Under these conditions propargylic alcohols **13** give rise to cyclic acetal **14**.



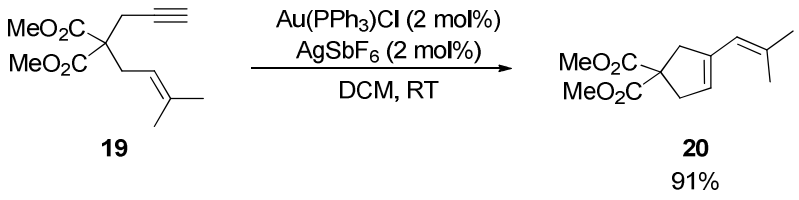
Scheme 4: Hydroalkoxylation of acetylenes

Another key transformation is the gold-catalysed intramolecular nucleophilic addition to propargylic acetates.[19] Cavallo *et al.* have shown that propargylic acetates can undergo 1,2- or 1,3-acyloxy migrations leading to the formation of vinyl gold(I) carbenoid species **16** or allene gold(I) complexes **17** which could be in rapid equilibrium (Scheme 5).[20] A double 1,2-shift, which also leads to **17** was found to be energetically more favoured than the direct 1,3-shift, although different substitution at the substrate could significantly influence this preference.



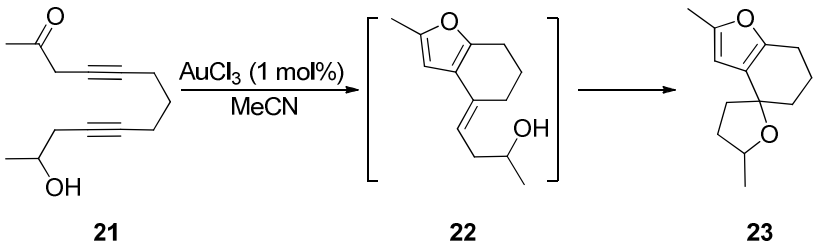
Scheme 5: Key intermediates in the propargylic migrations

In 2004, Echavarren highlighted that gold can be used in 1,6-enyne cycloisomerisations (Scheme 6). The catalyst employed $Au(PPh_3)^+$ was generated *in situ* from the reaction of $Au(PPh_3)Cl$ with $AgSbF_6$. This class of cycloisomerisation reaction is very useful in synthetic chemistry as it leads to diene products like **20** with functionality that can undergo further reaction.



Scheme 6: Enyne cycloisomerisation

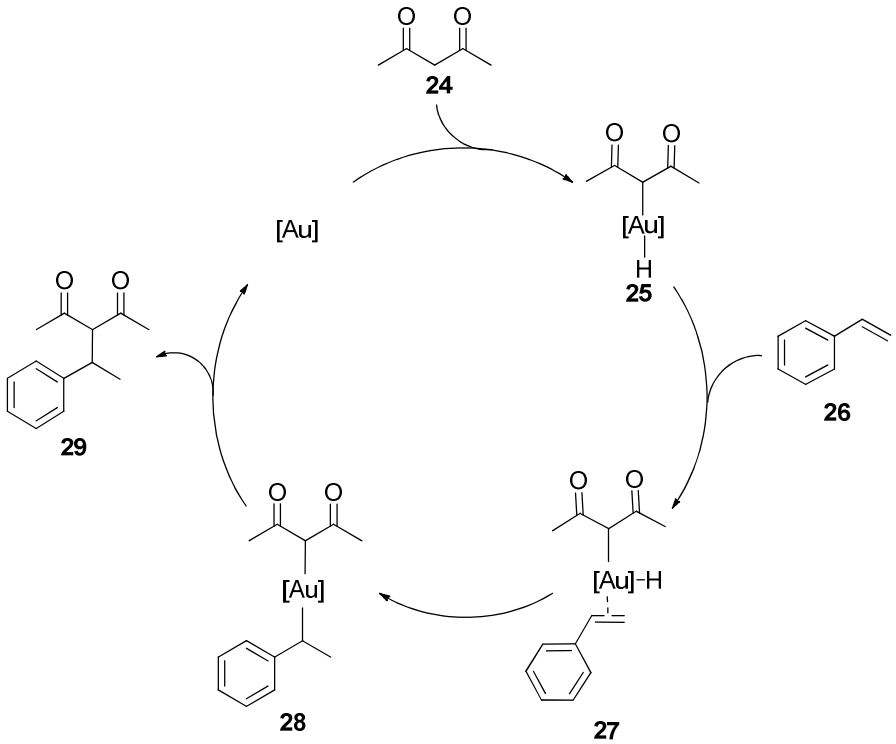
In 2000, the first gold-catalysed intramolecular addition of a hydroxy group to an activated alkene was reported by Hashmi *et al.* in the formation of the spirocycle **23** (Scheme 7).[21]



21 22 23

Scheme 7: Early example of intramolecular gold-catalysis

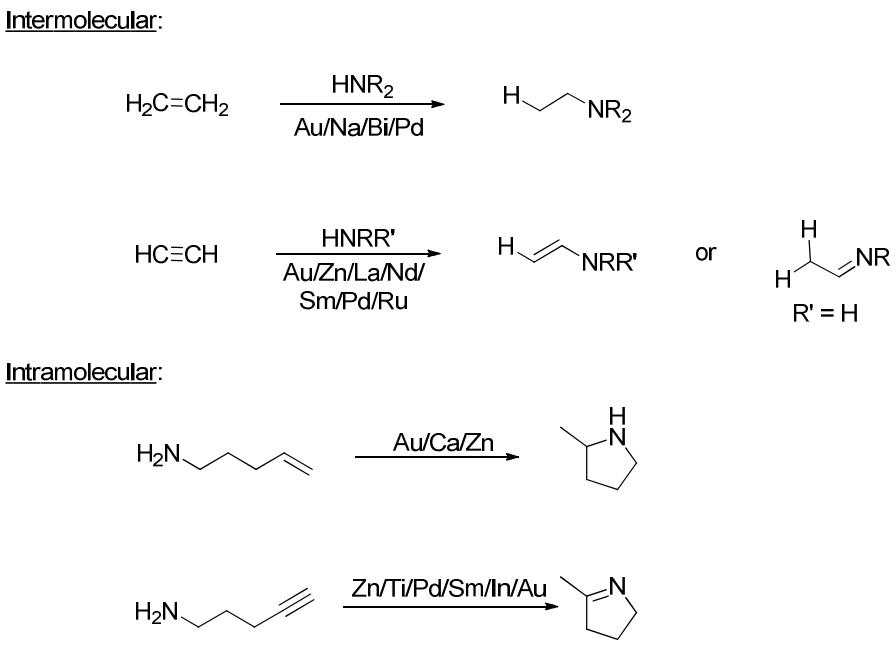
In 2004, Li *et al.* have shown C-C bond formation by the intermolecular addition of 1,3-diketones to styrenes in the presence of catalytic $AuCl_3$ and a silver salt.[22] The silver salt used affects the yield of the reaction and the absence of a silver salt leads to very low reactivity. Li *et al.* propose that the reaction proceeds *via* the activation of the C-H bond in the nucleophile *via* gold insertion (Scheme 8). However it is possible that the reaction proceeds by enolate addition to the alkene.



Scheme 8: Gold-catalysed ketone addition to styrenes

1.2 Hydroamination

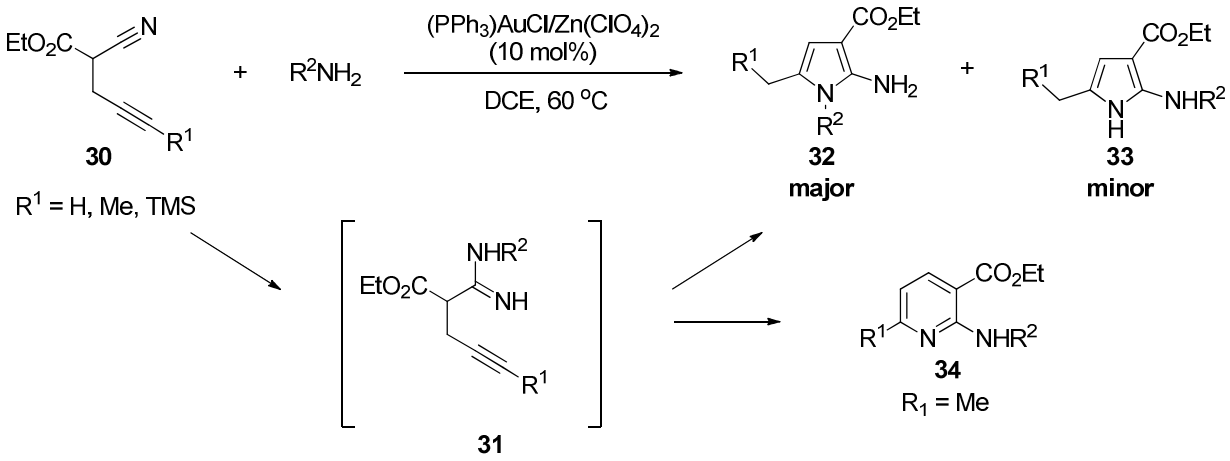
Hydroamination is the addition of a N-H bond across an unsaturated C-C bond (Scheme 9) and is important in the preparation of many compounds of chemical importance particularly pharmaceutical and speciality bulk chemicals. It is known that intramolecular hydroamination is more favourable than intermolecular hydroamination (kinetically and thermodynamically).[23]



Scheme 9: Examples of intermolecular and intramolecular hydroamination reactions of alkenes and alkynes

Hydroamination *via* noble metal catalysis is an atom economical method for the synthesis of amines and derivatives.[23-26] Transition metal-catalysed hydroaminations have been focussed on the use of early transition metals (groups 3-5) and late transition metals (groups 8-10).[23] For unactivated substrates, the functionality tolerated is limited, selectivities are modest and the slow rates of reaction are observed. Particularly, the hydroamination of unactivated alkenes remains limited, often needing higher temperatures.

It is known that gold can catalyse an intermolecular addition of a nitrogen containing compound prior to a cyclisation. This has been demonstrated by Demir *et al.* in the preparation of 2-aminopyrroles from 4-pentynenitriles (Scheme 10).[27]

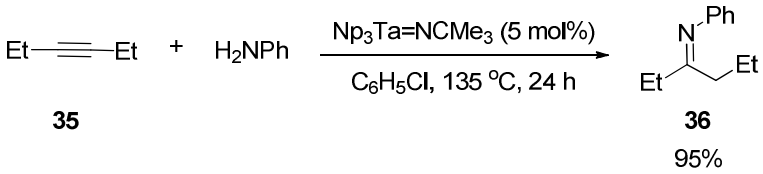


Scheme 10: Intermolecular hydroamination followed by a cyclisation

Other reactions can occur in which a diverse range of unsaturated functionalities are involved in different subsequent reactions instead of this ring closure step. Hydroamination of alkenes, alkynes *etc.*, have afforded many transformations including ring expansions, cyclisations and cycloisomerisations.[28] Alternatively the heteroatom can be introduced first and then undergo a subsequent cyclisation.

1.2.1 Hydroamination of alkynes

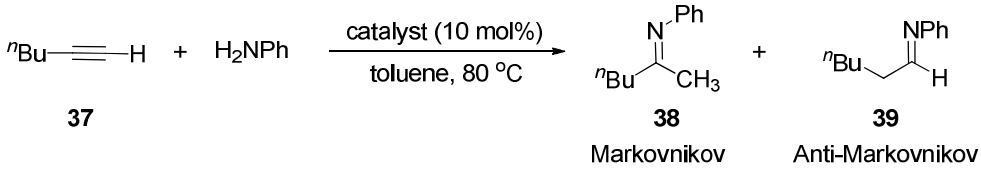
Arnold and Bergman have shown that tantalum can be employed for hydroamination reactions of alkynes with anilines (Scheme 11).[29] It should be noted that this required high reaction temperatures and lengthy reaction times. The yields were very low when aromatic substituents were introduced onto the alkyne.



35 **36** 95%

Scheme 11: Tantalum-catalysed hydroamination of an alkyne

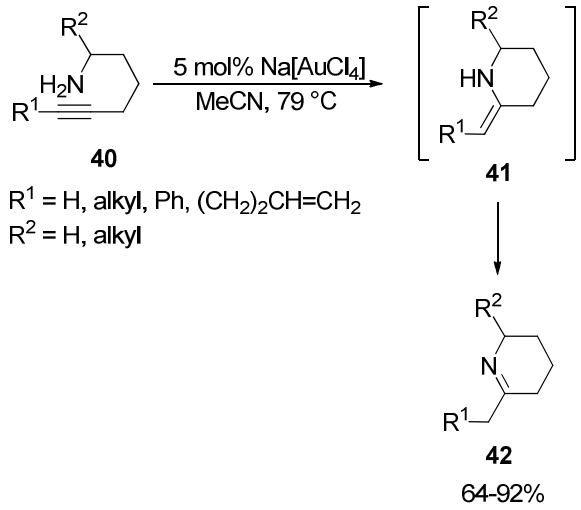
A similar hydroamination can be achieved using vanadium and titanium (Scheme 12). Lorber *et al.* have shown that vanadium catalysts gave better selectivity compared to titanium catalysts.[30] The highest yield (94%) was obtained when [Ti(NPh)(NHPh)$_2$] was used, with the highest selectivity 99:1 (Markovnikov/Anti-Markovnikov) achieved with V(carb)$_2$(NMe$_2$)$_2$.



37 **38** Markovnikov **39** Anti-Markovnikov

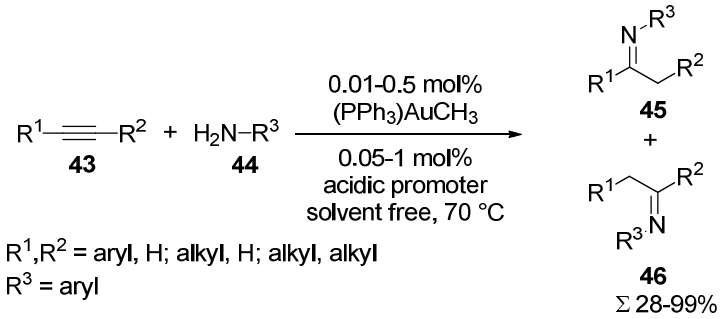
Scheme 12: Vanadium and Zirconium catalysed hydroamination

Utimoto *et al.* investigated the intramolecular hydroamination reaction of alkynes.[31] It was found that gold(III) catalysts were more effective than palladium(II) catalysts for the 6-exo-dig cyclisations (Scheme 13). Hydroamination initially gives the enamine intermediate **41** which undergoes tautomerisation to the more stable imine **42**. They used sodium tetrachloroaurate as the catalyst with loadings of 5 mol %.



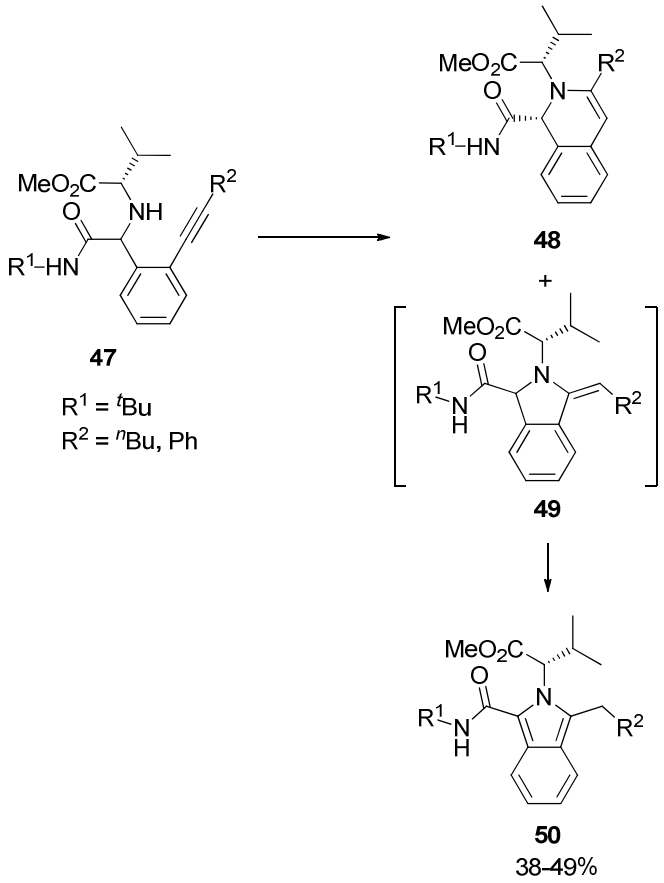
Scheme 13: Intramolecular hydroamination of alkynes

The first intermolecular gold-catalysed hydroamination was reported by Tanaka *et al.* forming imines from the corresponding alkyne and aniline substrates (Scheme 14).[32] With terminal alkynes Markovnikov regioselectivity was observed. $(Ph_3P)AuMe$ was used as catalyst in loadings as low as 0.01 mol% with $H_3PW_{12}O_{40}$ added as an acidic promoter. These reactions were carried out in solvent free conditions and were not successful when aliphatic amines were used. This was likely due to the Lewis basicity of the amines in this case.



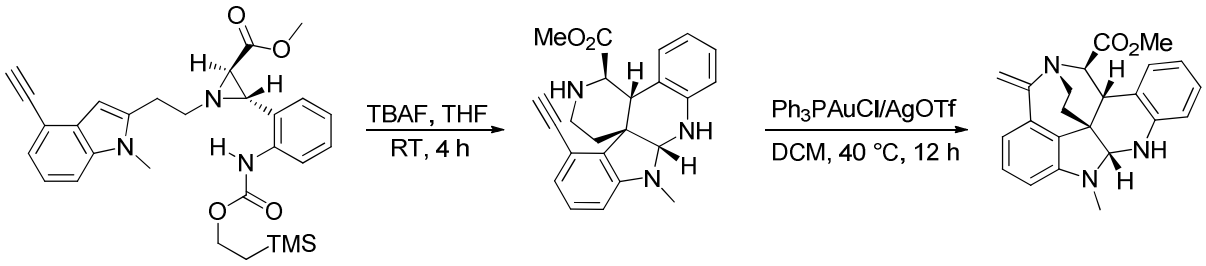
Scheme 14: First intermolecular gold-catalysed hydroamination

Dyker *et al.* have demonstrated that intermediate **47**, prepared from an Ugi four-component reaction, reacts to give the cyclic systems **48** and **50**.[33] The 6-*endo-dig* cyclisation affords **48** as only the diastereoisomer shown and the 5-*exo-dig* cyclisation affords **50**, arising from the aromatisation of the intermediate **49** (Scheme 15).



Scheme 15: Intramolecular hydroamination of an alkyne

Another example of an intramolecular hydroamination in a complex system is in the formation of the Communesin ring system **53** (Scheme 16) outlined by Crawley and Funk.[34] Compound **52** undergoes an intramolecular 7-*exo*-dig closure to afford the sterically encumbered enamine **53**.

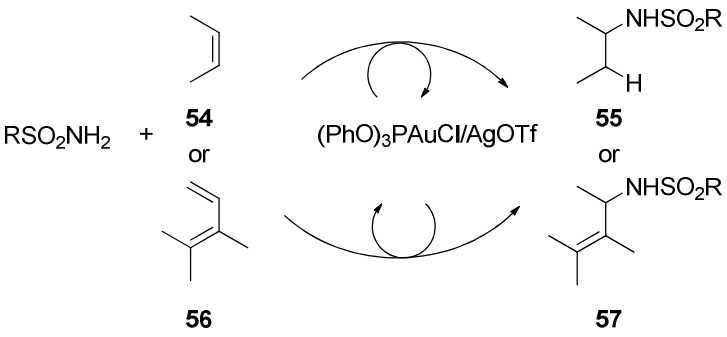


51 52 53

Scheme 16: Communesin ring formation

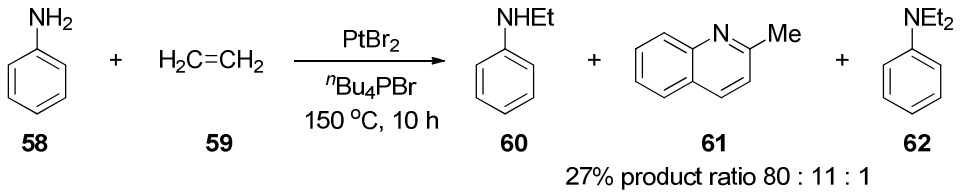
1.2.2 Hydroamination of alkenes

Hydroamination of alkenes using sulfonamides as the nitrogen source is often achieved by gold salts along with a silver salt co-catalyst, for example $AuPPh_3Cl/AgOTf$. Alkenes are less reactive to hydroamination compared to alkynes and allenes and therefore require higher reaction temperatures.[35] The active gold catalyst $PPh_3Au^+OTf^-$ is formed by counterion exchange. However, the disadvantage of this catalyst is the poor stability at high temperatures leading to the formation of gold mirror and nanoparticles.[14] Nájera *et al.* investigated different catalysts for the intermolecular addition of sulfonamides to alkenes and conjugated dienes (Scheme 17). They postulated that stronger electron-withdrawing ligands would increase the interaction of the LAu^+ with the C-C double bond and consequently a greater activity could be achieved. They have shown triphenylphosphitegold(I) chloride and silver triflate to be an efficient catalytic mixture for the transformation outlined in Scheme 17 as compared to the PPh_3 complex. Sulfonamides are considerably less nucleophilic than the corresponding amine and therefore less likely to interact unfavourably with the catalyst.



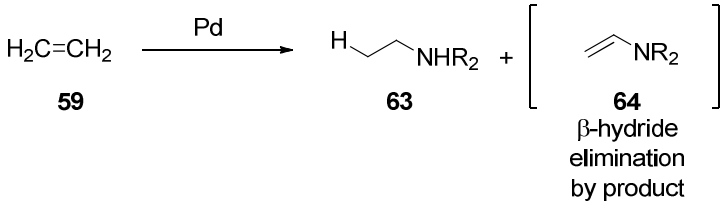
Scheme 17: Intermolecular addition of sulfonamides to alkenes and dienes

Coulson demonstrated that rhodium and iridium could be used for intermolecular hydroamination of ethene with secondary amines.[36] It has been shown that platinum salts give high turnover numbers for the addition of ethene to aniline (Scheme 18).[37] Anilines with electron-withdrawing substituents, therefore less basic, gave mostly the *N*-alkylated product **60** and less quinoline **61** was formed.



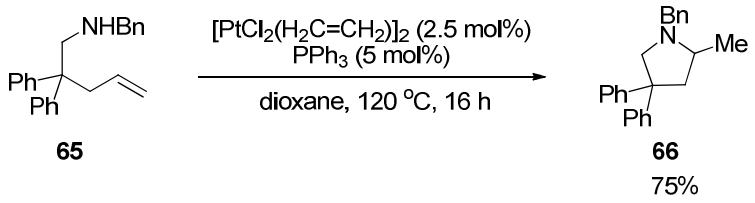
Scheme 18: Platinum catalysed hydroamination

Ruthenium[38], platinum[39, 40] and palladium[41-43] have been shown to catalyse such reactions but require fairly harsh conditions and in the case of palladium, β-hydride elimination usually occurs as a side reaction (Scheme 19).



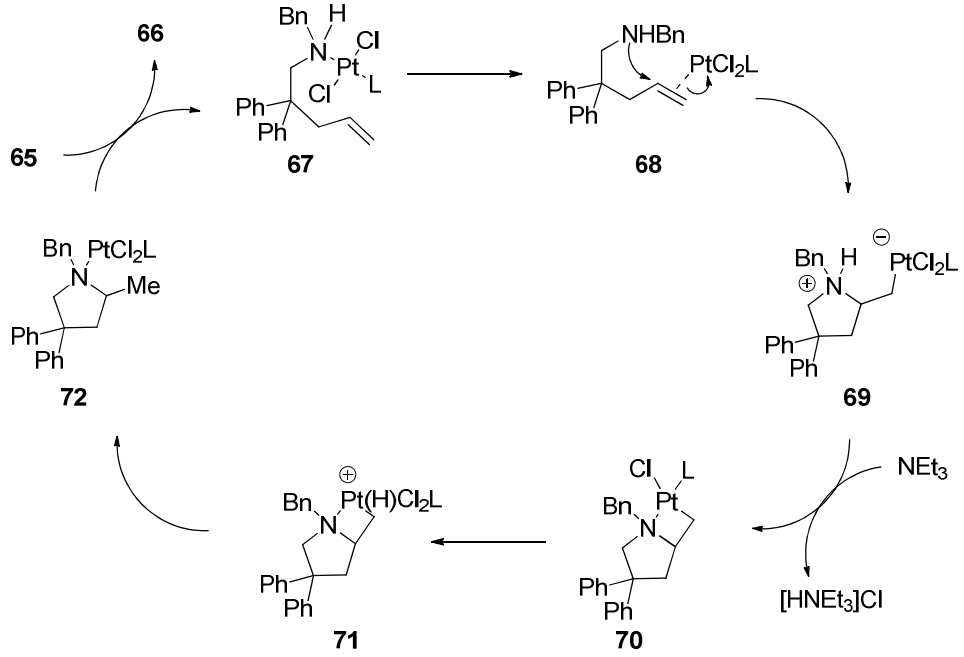
Scheme 19: β-hydride elimination by product

Widenhoefer and Bender have shown that platinum can be used for the intramolecular hydroamination of unactivated alkenes.[40]



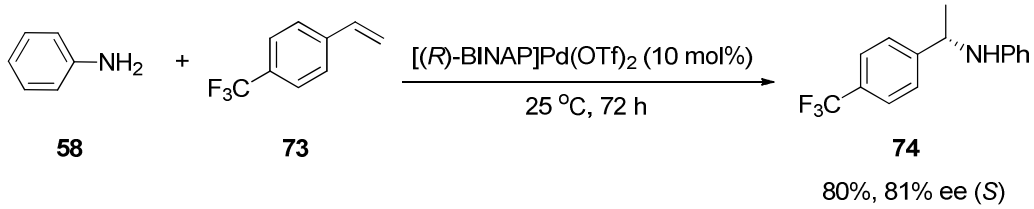
Scheme 20: Platinum-catalysed intramolecular hydroamination of unactivated alkenes

This reaction does not proceed for intermolecular systems such as ethylene with alkylamines. Mechanistically, C-N bond formation presumably occurs *via* intramolecular ligand exchange followed by outer-sphere attack of the pendant amine on the olefin of **68** to form **69** (Scheme 21). The next step is deprotonation/chloride displacement from **6** followed by intermolecular protonolysis of the Pt-C bond of **70**, presumably *via* a Pt(IV) hydride intermediate such as **71**. Ligand exchange from Pt-amine complex **72** would release **66** and regenerate **67**.



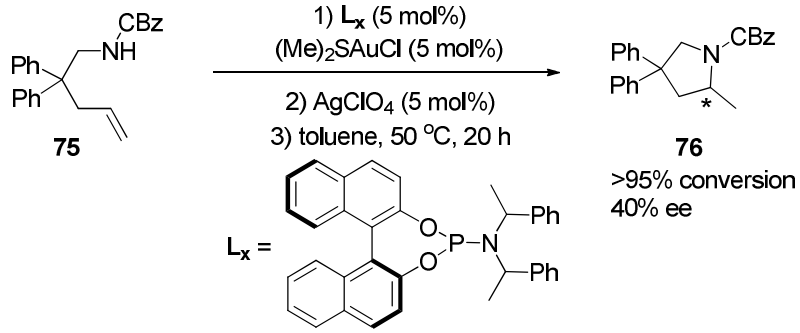
Scheme 21: Mechanism of platinum-catalysed hydroamination

Hartwig *et al.* have used enantiopure bisphosphines to provide nonracemic amine products (Scheme 22).[42] This also provides evidence that this reaction is irreversible.



Scheme 22: Asymmetric palladium-catalysed intermolecular hydroamination

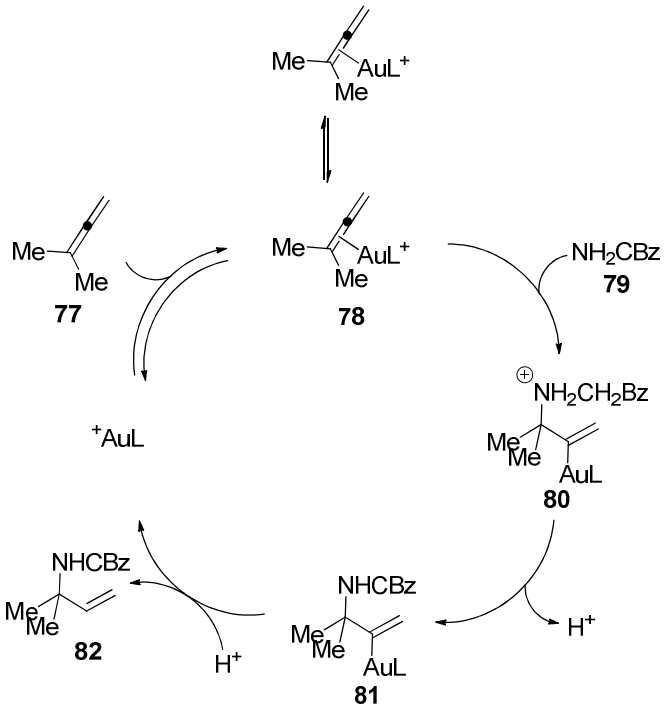
Michon and Agbossou-Niedercorn have shown that gold-catalysed asymmetric hydroamination of alkenes can be achieved with phosphoramidite ligands [44]



Scheme 23: Asymmetric hydroamination of alkenes

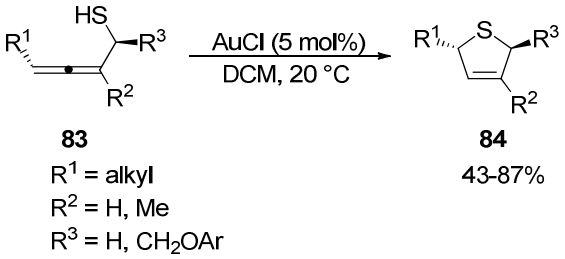
1.2.3 Hydroamination of allenes

Widenhoefer *et al.* investigated regioselectivity in the hydroamination of allenes using carbamates in the presence of gold(I) complexes (Scheme 24).[45] The Markovnikov adduct was formed at the more substituted terminus of the allene when a range of *N*-unsubstituted carbamates were reacted with monosubstituted, 1,1- and 1,3-disubstituted, trisubstituted and tetrasubstituted allenes.



Scheme 24: Mechanism of allene hydroamination

Hydrothiolation of allenes has been achieved by Krause *et al.* by the utilisation of AuCl under mild reaction conditions, to convert thiocarbinols to the corresponding 2,5-dihydrothiophenes (Scheme 25).[46]



Scheme 25: Hydrothiolation of allenes

1.3 Structure, synthesis and reactivity of allenes

Given that much of the work done in this project depends upon synthesis and reactivity of allenes, a brief summary of synthesis and properties of allenes is presented.

1.3.1 Structure and bonding of allenes

It is important to discuss the structure of allenes in order to understand their chemical reactivity (Figure 5). A molecular orbital treatment of the parent allene molecule correctly predicts that the most stable bonding arrangement involves two mutually perpendicular π-bonds, with the central atom (sp-hybridised) joined in a straight line to the two terminal carbon atoms (sp^2-hybridised).[47]

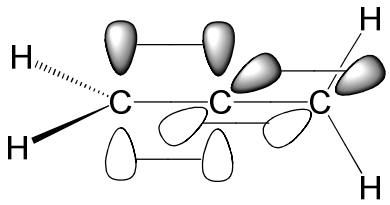


Figure 5: Arrangement of allenic π-bonds

In an unsubstituted allene the hydrogen atoms at one end of the molecule are projected above and below the plane containing the rest of the molecule. The two π-bonds are not co-planar and therefore are not conjugated. The C-C bond in an allene is known to undergo contraction with a bond length of 1.309 – 1.312Å compared to that of ethylene, 1.33Å. This is due to hyperconjugation (σ-π overlap) which suggests partial triple bond character.

Allenes with two different substituents on the sp^2-hybridised carbon will have axial chirality. This can be determined by considering the substituents on the front atom

followed by the back atom when viewed along the allene axis. The priority of the groups is assigned according to the Cahn-Ingold-Prelog priority rule.

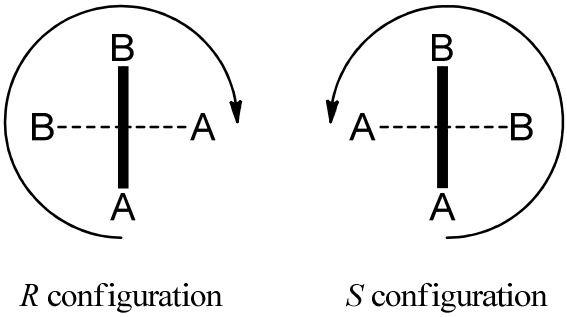


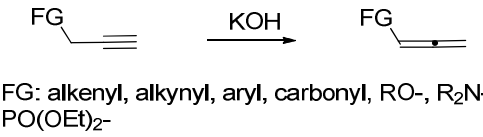
Figure 6: Chirality of allenes

Since the prediction of allenes by Van't Hoff in 1875,[48] many efforts have been made to synthesise allenes. The first allene synthesis was reported by Burton and von Pechmann in 1887.[49] It was thought that this class of compound was highly unstable and this hampered the development of allene chemistry.[50]

1.3.2 Synthesis of allenes

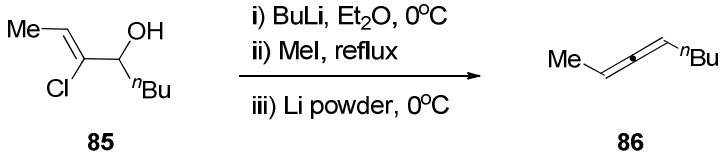
Allenes have many applications as building blocks in organic chemistry.[51] With interest increasing in allene chemistry there has been a focus on developing facile synthetic pathways to access these useful intermediates. Allenes have the potential to undergo regio- and stereoselective C-C and C-X bond forming transformations.[52]

The most commonly used starting material in the synthesis of allenes is their alkyne isomers (Scheme 26). This is reflected in the early methods for the synthesis of allenes such as isomerisation of the FG-CH_2-C≡C moiety in the presence of a base.[53]



Scheme 26: Allene synthesis by alkyne isomerisation

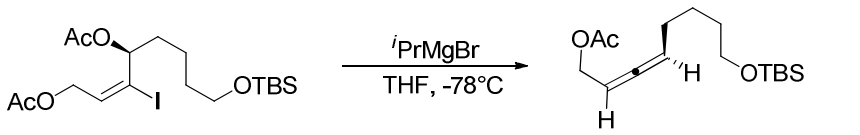
Allenes can also be prepared from functionalised alkene precursors *via* a 1,2-elimination (Scheme 27), such as a dehydrohalogenation of 2-halopropene derivatives.[54]



85 **86**

Scheme 27: Elimination reactions to give allenes

Wu *et al.* have shown that using Knochel's Mg-Br exchange protocol, it is possible to prepare 1,3-disubstituted enantioenriched allenes from optically active alkenyl iodides **87** in good yield and high stereoselectivity (Scheme 28).[55] (*S*,*E*)-8-((*tert*-butyldimethylsilyl)oxy)-3-iodooct-2-ene-1,4-diyl diacetate **87** was converted, with highly efficient chirality transfer from the allylic stereogenic centre to the allene axis, to the product **88**.



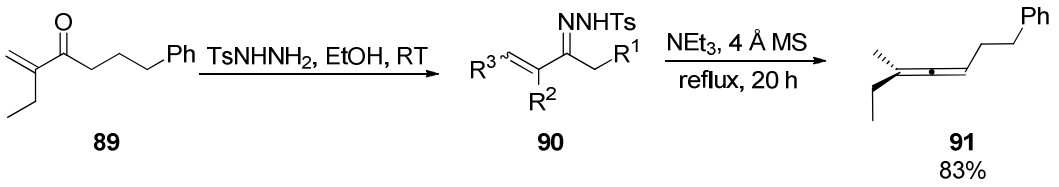
87 **88**

90% ee 93%, **88**(ee)/**87**(ee) >99%

Scheme 28: Knochel's Mg-Br exchange protocol

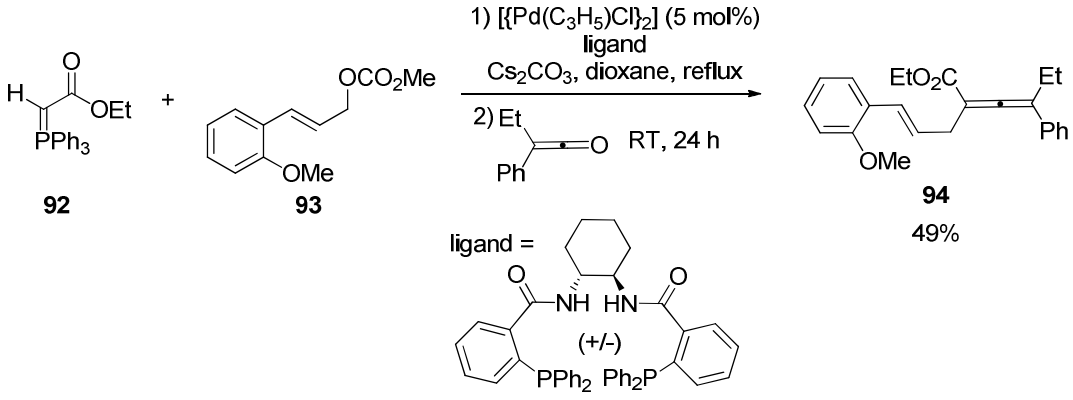
Tu *et al.* have developed a one-pot synthesis of substituted allenes from enones (Scheme 29). Tosylhydrazone derivatives are generated *in situ* from *α,β*-unsaturated enones which

then undergo a loss of N_2 and an intramolecular H-transfer of the diazene intermediate to give the desired allene.[56]



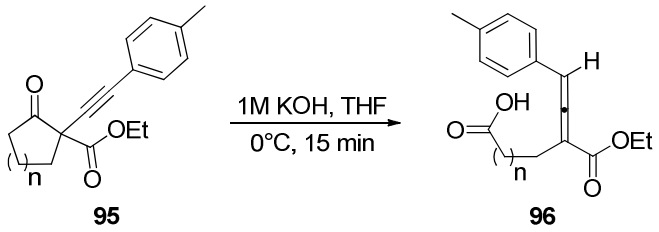
Scheme 29: One-pot synthesis of allenes from enones

The Wittig reaction has also been employed in the synthesis of allenes by reacting phosphorus ylides with ketenes (Scheme 30). Palladium-catalysed allylic alkylation in the presence of a Pd/Trost racemic ligand system afforded a new class of allylic phosphorus ylides which reacted with various ketenes giving rise to tetrasubstituted allenes in good overall yields.[57]



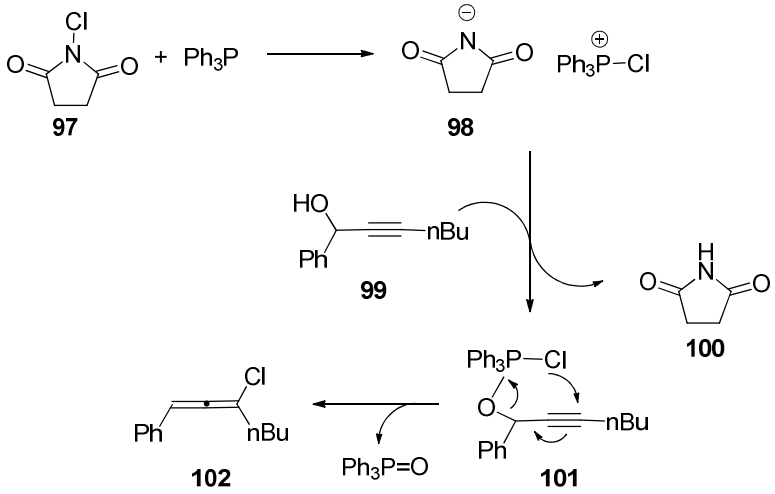
Scheme 30: Wittig reaction for allene preparation

Nagao *et al.* have shown that by utilising a retro-Dieckmann-type reaction of α-alkynyl-α-ethoxy-carbonyl cyclopentanone and cyclohexanone derivatives, under basic conditions, can also produce allenes (Scheme 31).[58]



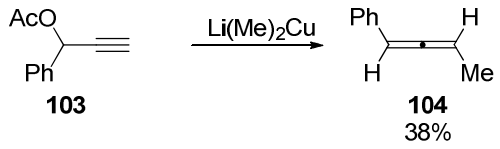
Scheme 31: Retro-Dieckmann-type reaction

Haloallenes have been prepared from propargyl alcohols with *N*-halosuccinimides and triphenylphosphine (Scheme 32).[59] This is a mild method for the synthesis of haloallenes and tolerates a diverse range of aromatic substituents on the propargyl alcohols.



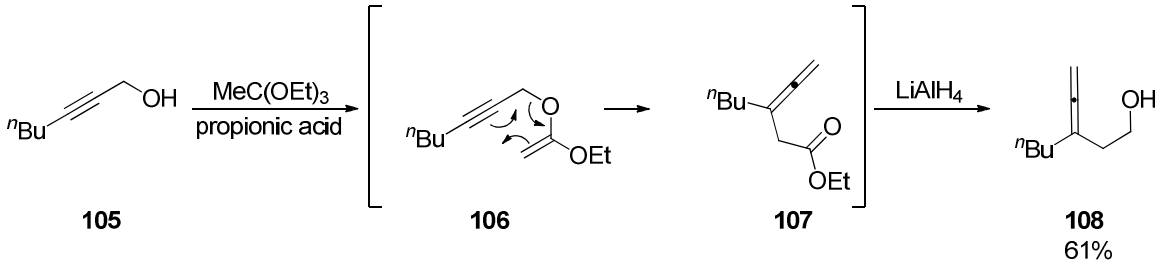
Scheme 32: Mechanism for haloallene formation

Crabbé has shown organocopper reagents can be employed to transform 1-ethynylcycloalkanol acetates to alkyl allenes.[60] $LiMe_2Cu$ and Li-*n*-Bu_2Cu were used as the reagents in this transformation (Scheme 33). The allene system is formed due to the synergistic effect brought about by the reagent, acting on the triple bond and the acetoxyl group. This early work of Crabbé does not tolerate unprotected alcohol groups in the substrate which was disadvantageous for our studies. (*vide infra* Chapter 3, Scheme 62)



Scheme 33: Early Crabbé allene synthesis

Preparation of allenes can also be achieved by the Johnson-Claisen rearrangement, a powerful carbon-carbon bond forming reaction (Scheme 34).[61-63] Allenic alcohols can be generated by reaction of the propargyl alcohol in the presence of triethylorthoacetate to afford the propargyl vinyl ether which undergoes a [3,3]-sigmatropic rearrangement to give the allenic ester which is subsequently reduced to the allenic alcohol.[64]



Scheme 34: Mechanism of Johnson-Claisen reaction of propargyl alcohols

1.4 Sulfamidate chemistry

Our experimental endeavours will focus on gold-catalysed hydroamination to produce sulfamidates and a review of the current uses of sulfamidates is given. Furthermore, it was important to consider the current methods of sulfamidate formation and the limitations therein.

Cyclic sulfamidites and sulfamidates are useful intermediates for the preparation of functionalised amines (Figure 7). Cyclic sulfamidites are key intermediates in the production of antimicrobial agents used in deodorants and shampoos.[65]

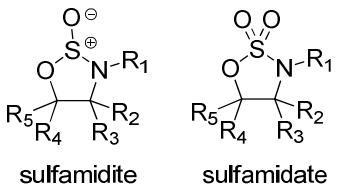
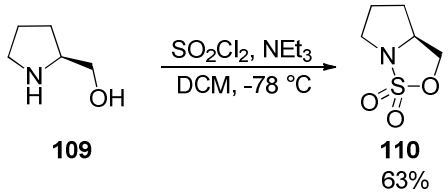


Figure 7: Sulfamidite and sulfamidate compounds

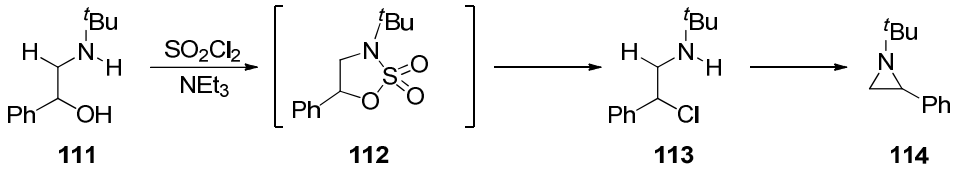
1.4.1 Synthesis of sulfamidates

Synthesis of cyclic sulfamidates from the corresponding amino alcohol with a reagent which directly installs the $–SO_2-$ moiety would appear the most direct synthetic route. However, approaches based upon the use of sulfuryl chloride or sulfuryl diimidazole have been unsuccessful on the whole with only the desired sulfamidate produced in cases involving conformationally constrained 1,2- amino alcohols, such as prolinol and amino sugar variants (Scheme 35).[66, 67] Prolinol reacts with sulfuryl chloride to afford the desired sulfamidate, but notably only at low temperatures. There are very few examples of similar processes.



Scheme 35: Sulfamidate synthesis from prolinol

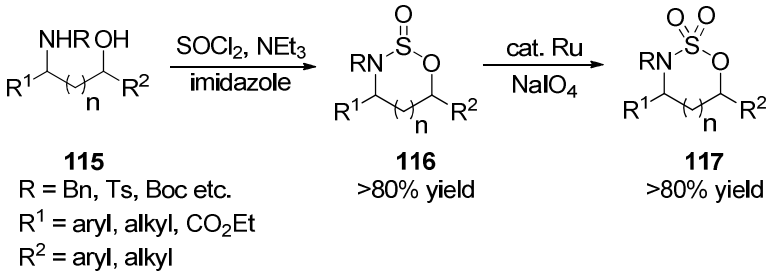
Competing aziridination has also been seen with attempts to form sulfamidates directly from 1,2-aminoethanols and sulfuryl chloride.[69, 71] Deyrup *et al.* have shown that the desired sulfamidate could not be isolated when 1-phenyl-2-*t*-butylaminoethanol was reacted with sulfuryl chloride. Small amounts of the 1-*t*-butyl-2-phenylaziridine were formed (Scheme 36).



111 **112** **113** **114**

Scheme 36: Competing aziridination in sulfamidate formation

Treatment of 1,2- or 1,3-amino alcohols with thionyl chloride in the presence of imidazole as a nucleophilic catalyst leads to the efficient formation of 1,2- and 1,3- cyclic sulfamidites as a mixture of epimers at sulphur (Scheme 37).[68,69] The resulting sulfamidite is then oxidised to the corresponding sulfamidate by one of many methods, *m*-CPBA[67] and $KMnO_4$[70] have been employed as oxidants, however the use of catalytic RuO_4, $RuCl_3$ and $NaIO_4$ in aqueous solvent produces the desired sulfamidate in yields greater than 80%.



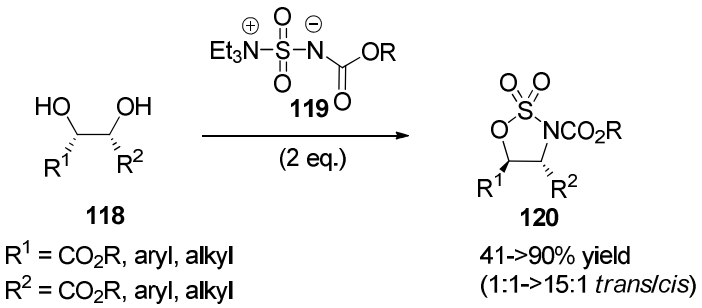
115
R = Bn, Ts, Boc etc.
R^1 = aryl, alkyl, CO_2Et
R^2 = aryl, alkyl

116
>80% yield

117
>80% yield

Scheme 37: Synthesis of sulfamidates from amino alcohols

This method of formation requires isolation of the sulfamidite species prior to oxidation as both triethylamine and imidazole inhibit ruthenium oxidants.[72] Functionality is limited to that which can withstand the harsh oxidation conditions therefore sulfamidates bearing alkene moieties cannot be prepared using this method.

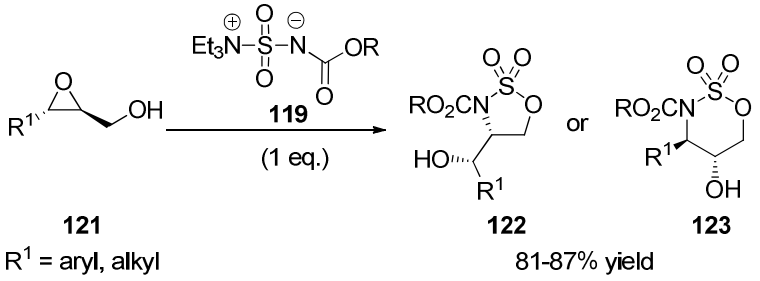


Scheme 38: Utilisation of the Burgess reagent in sulfamidate formation

Nicolaou and co-workers have employed a double alcohol activation mechanism to form 1,2-cyclic sulfamidates from the corresponding 1,2-diols by utilising the Burgess reagent **119** (Scheme 38).[73] Double sulfonylation was proposed to convert the diol to an intermediate which undergoes cyclisation *via* an S_N2 mechanism with departure of the better leaving group. Limitations in regiochemistry of the product are dependent on the stereoelectronic preferences of the substrates involved. A range of modified Burgess-type reagents allow access to different classes of *N*-carbamate-protected cyclic sulfamidates.

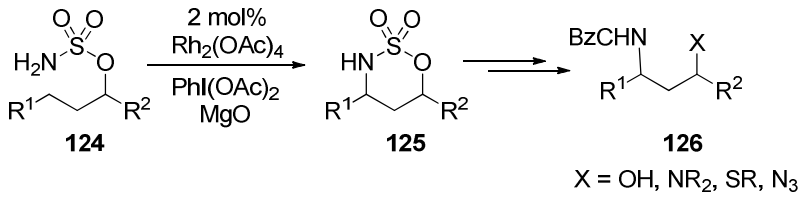
Many 1,2-diols are available in an enantioenriched form and this method allows direct conversion to the electrophile which can undergo several further transformations. This chemistry has been further exploited by Nicolaou to enable the formation of either 5- or 6-ring cyclic sulfamidates (substrate dependent) from allylic alcohol-derived epoxides.[74]

Hudlicky *et al*. have shown that the Burgess reagent **119** can be used to convert simple epoxides to the corresponding 5-ring cyclic sulfamidates but in modest yields (Scheme 39).[75]



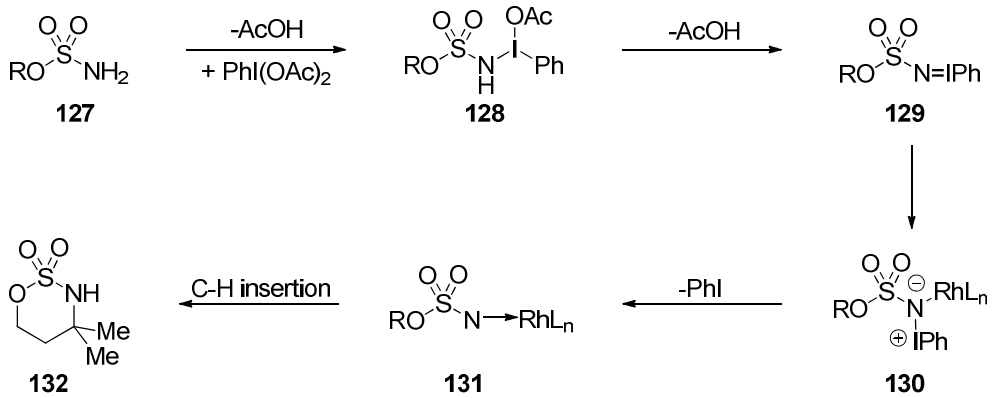
Scheme 39: Preparation of sulfamidates from epoxides

Du Bois *et al.* have demonstrated that Rh-catalysis can afford cyclic sulfamidates by intramolecular amidation of C-H bonds (Scheme 40).[76] This is achieved through γ-C-H bond amination. The appropriate alcohol is reacted with sulfamoyl chloride which is formed *in situ* from formic acid and chlorosulfonyl isocyanate to yield the desired sulfamate ester. This cyclisation favours the formation of 6-membered rings but where this is not possible 1,2-cyclic sulfamidates are formed.



Scheme 40: Rh-catalysis for the preparation of sulfamidates

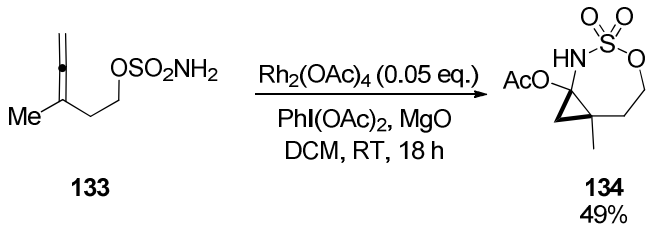
Du Bois has shown that a Rh-nitrene intermediate **131** is key in sulfamidate formation (Scheme 41).[77] The oxidant complex could present in many forms including the iminoiodinane **129**. The iminoiodinane **129** will react quickly with the rhodium catalyst to form the nitrene which will undergo a C-H insertion to afford the sulfamidate **132**.



Scheme 41: Proposed mechanism for Rh-nitrene formation

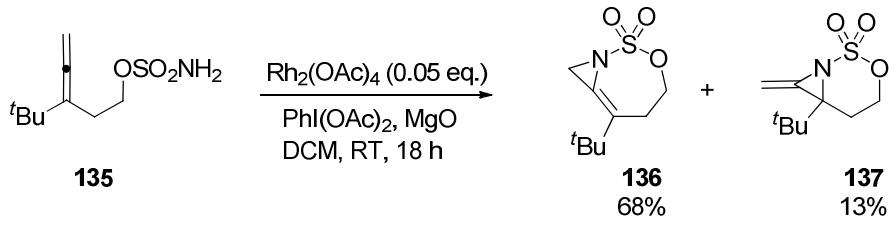
The bias towards formation of the oxathiazinane can be accounted for by the elongated S-O and S-N bonds (1.58 Å) and the obtuse N-S-O angle (103°) of the sulfamate, which

match closely the metrical parameters of the heterocycle. The catalyst is commercially available and the reaction is high yielding. Silver-catalysed protocols have also been reported.[78] When there are two different γ-C-H bonds the rate of reaction is tertiary C-H bonds > secondary/benzylic/allylic > primary C-H bonds.



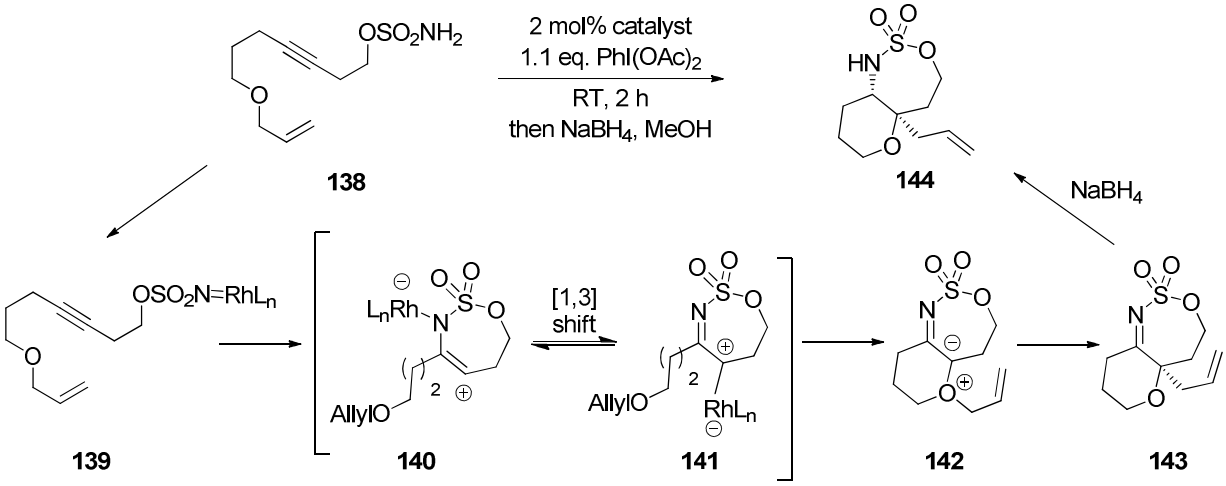
Scheme 42: Rh-catalysed aminations of allenic sulfamates

Robertson *et al.* have shown that Rh-catalysed intramolecular amination of allenes can be used to form the 1-acetoxy-1-aminocyclopropane **134** from allene **133** (Scheme 42).[79] This reaction currently proceeds in moderate yields with the products having limited further reactivity. When the methyl group is replaced with the bulkier *tert*-butyl group, a cyclic enamine by-product is observed (Scheme 43).



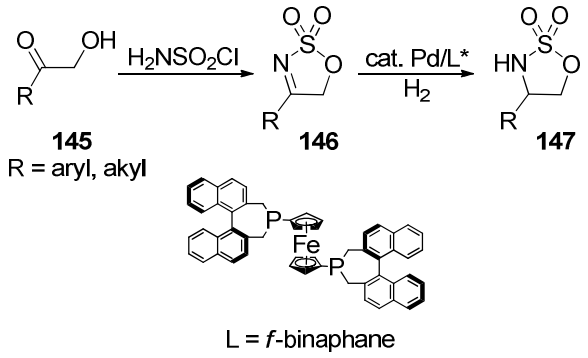
Scheme 43: Enamine by-product produced with bulky substituents

Blakey has shown that sulfamidates can be synthesised *via* a metallonitrene intermediate.[80] This metallonitrene/alkyne metathesis reaction proceeds through a zwitterionic intermediate which then undergoes a [1,3] metal shift to complete the metathesis, generating an imine which undergoes a further C-O bond forming cascade reaction.



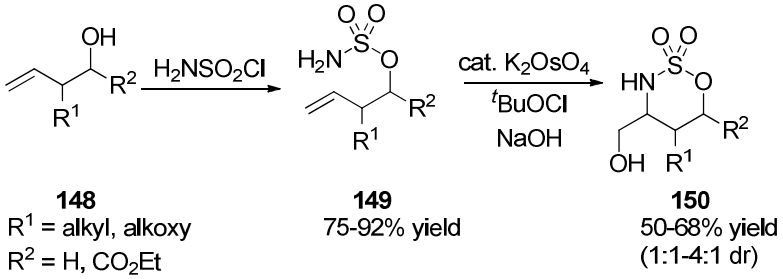
Scheme 44: Proposed mechanism for the Rh(II)-catalysed cascade reaction

Zhou *et al.* have shown that enantioenriched 1,2-cyclic sulfamidates can be prepared by asymmetric hydrogenation of an imine precursor (Scheme 45) .[81] Aryl- and alkyl-substituted α-hydroxyketones when treated with sulfamoyl chloride afforded the corresponding cyclic imines after acid-promoted condensation. Hydrogenation of the imine product **146** using a Pd-catalyst modified with *f*-binaphane, a chiral ferrocene-derived *bis*-phosphine, affords the corresponding *N*-unsubstituted cyclic sulfamidates **147** in near quantitative yields, and with excellent levels of asymmetric induction. This method is limited to the synthesis of 1,2-cyclic sulfamidates with substituents at the nitrogen bearing carbon only.



Scheme 45: Preparation of sulfamidates *via* imines

Donohoe had previously investigated tethered aminohydroxylation of allylic carbamates.[82] Kenworthy and Taylor adapted this method to prepare sulfamidates from the reaction of homoallylic alcohols with an osmium catalyst, providing a route to 6-membered cyclic sulfamidates possessing pendant alcohols (Scheme 46).[83] This proceeds in modest yields and does not tolerate substituted alkenes.



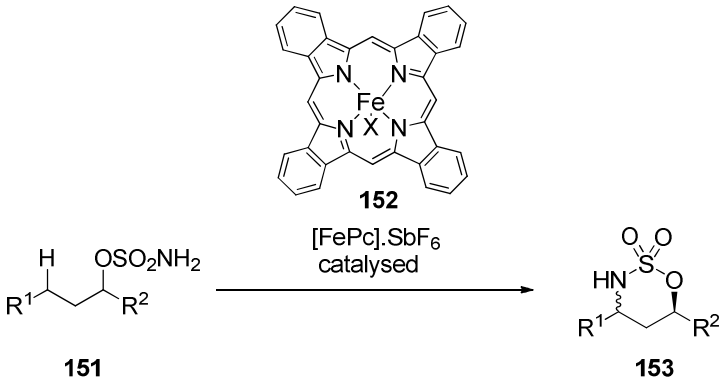
148
R^1 = alkyl, alkoxy
R^2 = H, CO_2Et

149
75-92% yield

150
50-68% yield
(1:1-4:1 dr)

Scheme 46: Cyclic sulfamidate bearing a pendant alcohol

Paradine and White have employed iron-catalysis in the synthesis of cyclic sulfamidates (Scheme 47).[84] An iron phthalocyanine complex [FePc]Cl, an inexpensive industrial ink additive, was the most effective catalyst in their screen.



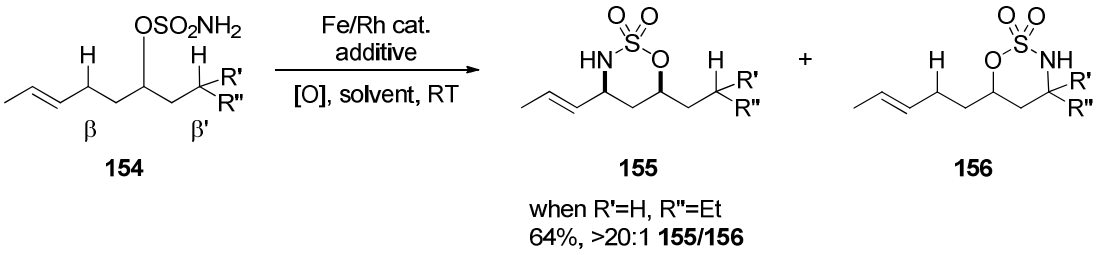
151

153

Scheme 47: Iron-catalysis for sulfamidate preparation

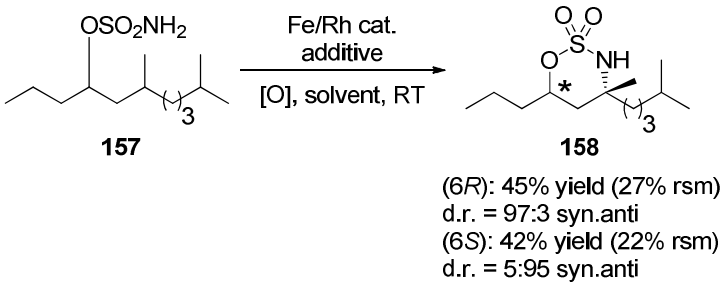
This catalyst has a strong preference for allylic C-H amination over aziridination and all other C-H bond types. Scheme 48 shows that there are two possible sulfamidate products

from either reaction at the β or β' position and the most reactive C-H bond will undergo amination. (i.e. allylic > benzylic > ethereal > 3° > 2° >> 1°)



Scheme 48: Reactivity trends for allylic C-H amination

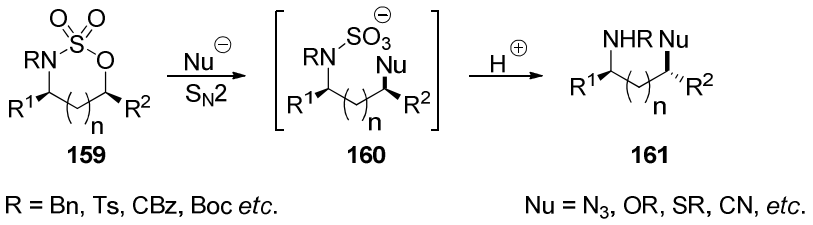
Moreover, in polyolefinic substrates, the site selectivity can be controlled by the electronic and steric character of the allylic C-H bond. Although this reaction is shown to proceed *via* a stepwise mechanism, the stereoretentive nature of the C-H amination of 3° aliphatic C-H bonds suggests a very rapid radical rebound step (Scheme 49).



Scheme 49: Amination of tertiary aliphatic C-H bonds to give stereospecific formation of sulfamidates

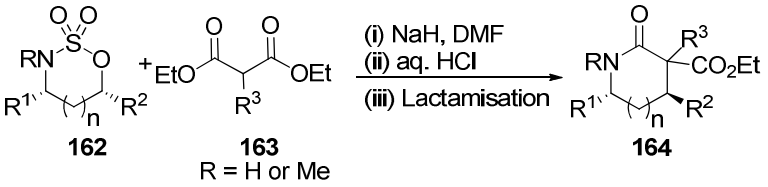
1.4.2 Reactivity of sulfamidates

Cyclic sulfamidates are versatile electrophiles. Nucleophilic attack occurs at the oxygen bearing carbon *via* an S_N2 mechanism to provide an *N*-sulfate intermediate which is then hydrolysed to give a substituted amine (Scheme 50).[85]



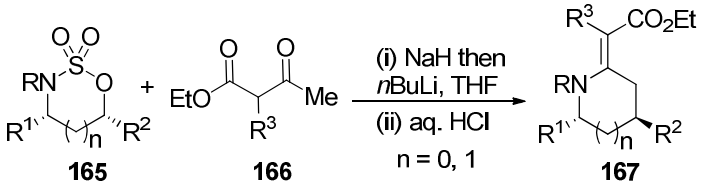
Scheme 50: Nucleophilic ring opening of cyclic sulfamidates

Lactams can be synthesised from a range of cyclic sulfamidates undergoing reaction with the sodium enolate of dialkyl malonates in DMF (Scheme 51).[86] 5-Membered cyclic sulfamidates are more reactive than 6-membered cyclic sulfamidates due to ring strain. Gallagher *et al.* have shown that higher temperatures and longer reaction times were required to effect C-O bond cleavage of the 6-membered sulfamidates. After the formation of the C-C bond, a small amount of aqueous HCl hydrolyses the *N*-sulfate and induces lactam formation. Formation of 5-membered cyclic sulfamidates is more facile than the 6-membered counterparts.



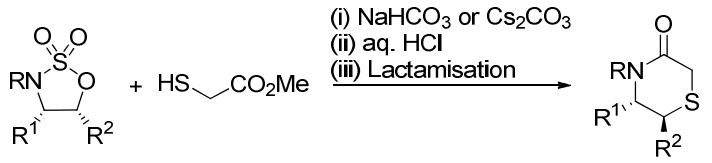
Scheme 51: Preparation of lactams from sulfamidates

Alkylidene pyrrolidines have been prepared from the opening of cyclic sulfamidates with the dianion of ethyl acetoacetate (Scheme 52). Nucleophilic cleavage occurs with moderate ease, *N*-sulfate hydrolysis is followed by condensation to give the target **167**.



Scheme 52: Preparation of alkylidene pyrrolidines from sulfamidates

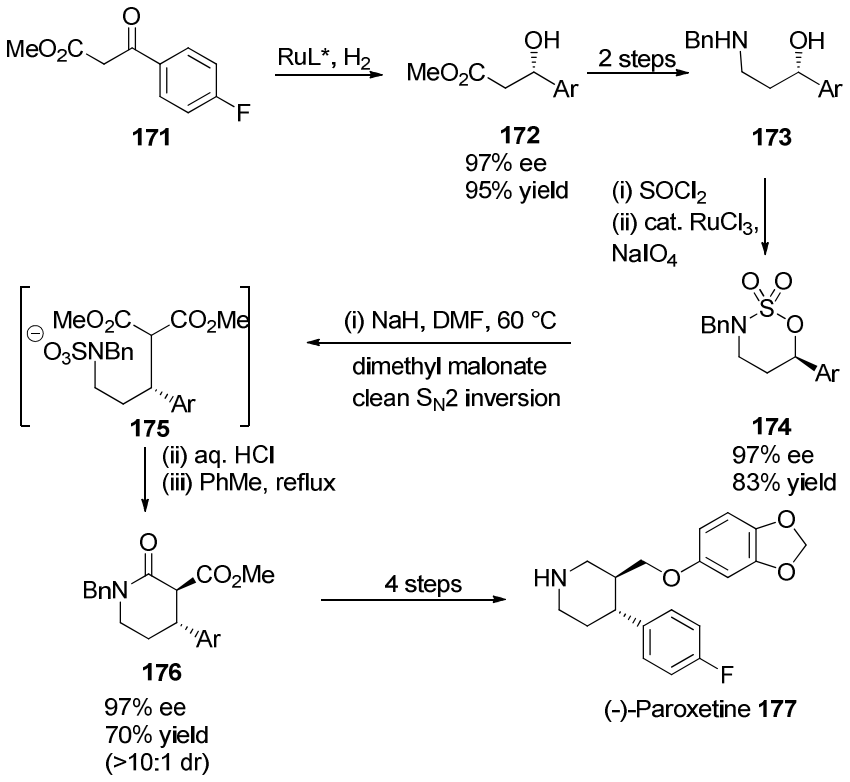
Gallagher *et al.* have also shown that thiomorpholines have been prepared from the corresponding 1,2-cyclic sulfamidates (Scheme 53). Reaction with a thiol possessing a pendant ester can undergo nucleophilic ring cleavage, *N*-sulfate hydrolysis followed by cyclisation to give substituted and enantioenriched thiomorpholines. Bulky substituents on the cyclic sulfamidate are tolerated and give rise to the corresponding thiomorpholines in excellent yields.



Scheme 53: Preparation of thiomorpholines from sulfamidates

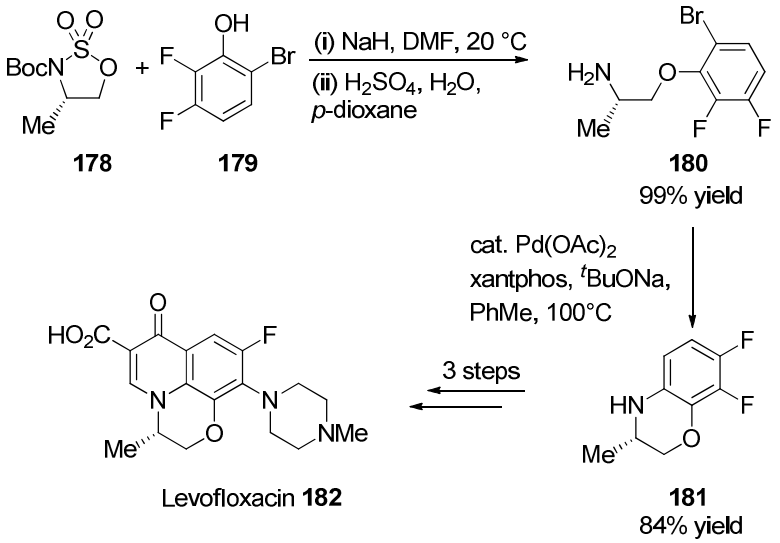
1.4.3 Sulfamidates in target synthesis

Piperidines are part of a therapeutic heterocyclic class and it is of interest to access enantiopure 3,4-disubstituted piperidines.[87] Sulfamidate chemistry has been used in the synthesis of the anti-depressant (-)-paroxetine. Gallagher *et al.* have demonstrated cleavage of the C-3-*aryl*-substituted 1,3-cyclic sulfamidate with an enolate nucleophile.[88] The route to (-)-paroxetine (Scheme 54) involves asymmetric hydrogenation of β-ketoester **171** affording alcohol **172** in excellent yield and high enantiopurity. With amino alcohol **174** in hand, the sulfamidate **174** can be prepared by treatment of **173** with $SOCl_2$ followed by Ru-catalysed oxidation. Treatment of this species with the anion of malonate, followed by *N*-sulfate hydrolysis and thermally promoted lactamisation delivers the target 3,4-disubstituted piperidinone **176** in excellent yield and with no detectable loss of enantiopurity, thereby demonstrating clean S_N2 cleavage of the C-3-*arylated* 1,3-cyclic sulfamidate. Intermediate **176** is then easily converted to (-)-paroxetine **177**.



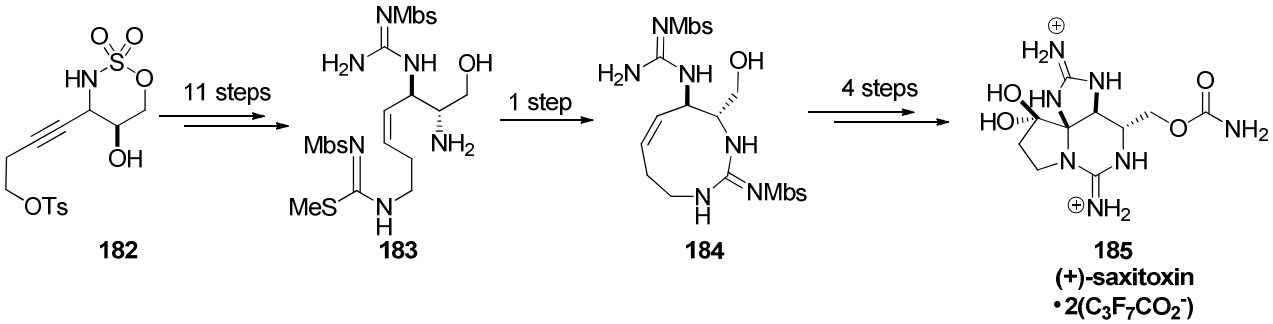
Scheme 54: Synthesis of paroxetine

(-)-Levofloxacin **182** is an antibiotic drug which is active against both gram-positive and gram-negative bacteria and is prescribed for a wide range of infections.[89] The biggest synthetic hurdle faced in the synthesis of Levofloxacin is identifying a concise asymmetric entry to the chiral benzoxazine core **181** (Scheme 55). Alanine-derived cyclic sulfamidate **178** was reacted with phenol **179**. Treatment of cyclic sulfamidate **178** with the anion of **179** resulted in the smooth nucleophilic ring cleavage to generate adduct **180** in essentially quantitative yield. In this case concomitant removal of both the *N*-sulfate and *N*-Boc moieties could be achieved in the same pot by employing 10% H_2SO_4 in dioxane for the hydrolysis step. Exposure of **180** to Pd(0)-mediated ring closure conditions then cleanly afforded the core **181** of levofloxacin **182** in 84% yield. Conversion of this intermediate to Levofloxacin in three further steps has been reported.[90]



Scheme 55: Synthesis of Levofloxacin

Du Bois has shown a stereoselective synthesis of (+)-saxitoxin, a paralytic shellfish poison, *via* a sulfamidate intermediate.[91]



Scheme 56: (+)-Saxitoxin synthesis

Sulfamidates have widespread application in organic synthesis. With recent advances in the synthesis of cyclic sulfamidates from common starting materials they are becoming ever more useful building blocks. Sulfamidates can undergo reaction to give a wide range of diverse intermediates that are important precursors of chemically and biologically important molecules.

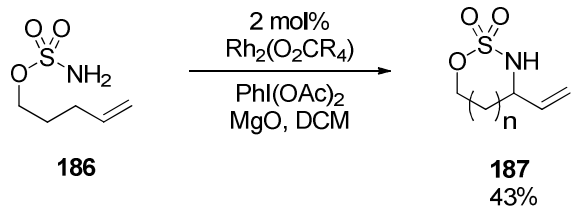
Initial investigations into novel sulfamidate formation was focussed on use of the Burgess reagent. In Chapter 2 we outline the attempts at reversal of regioselectivity in sulfamidate synthesis.

Chapter 2

Attempted Reversal of the Regioselectivity in the Burgess-Reagent Mediated Sulfamidate Synthesis

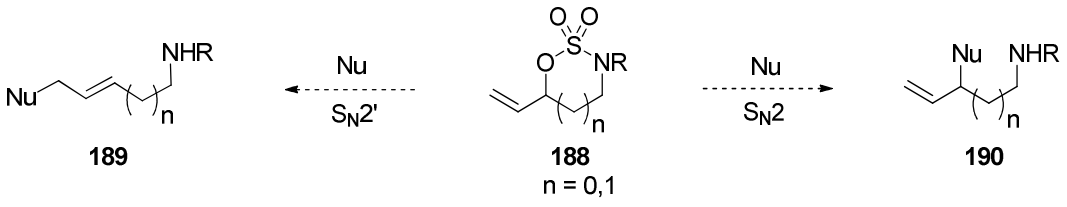
Chapter 2: Attempted reversal of the regioselectivity in the Burgess-Reagent mediated sulfamidate synthesis

There are relatively few examples of simple vinyl-substituted sulfamidates known in the literature (Scheme 57). Du Bois has shown that 6-membered cyclic sulfamidate **187** can be synthesised using Rh or Ru catalysis (Scheme 57).[91] White has also synthesised similar sulfamidates using Fe catalysis.[84] The most common method for sulfamidate formation involves the synthesis of the sulfamidite which is then subsequently oxidised to the sulfamidate.[67-70] The harsh oxidation conditions required to convert the sulfamidite intermediate to the sulfamidate are not compatible with alkenes (Scheme 36, Chapter 1).



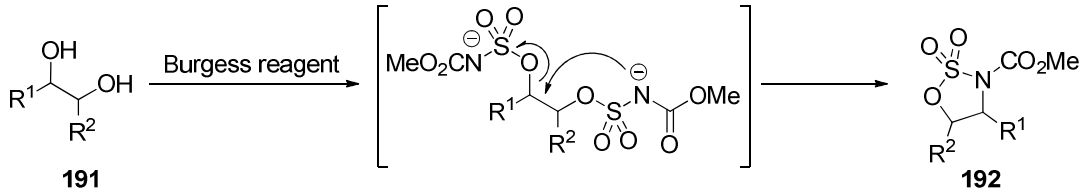
Scheme 57: Simple vinyl-substituted sulfamidates

Synthesis of sulfamidates **188** with vinyl groups on the oxygen-bearing carbon (not currently known in the literature) (Scheme 58) would be of interest as this functionality would provide a means by which to access a wide range of different compounds. Nucleophilic attack typically occurs at the oxygen bearing carbon (S_N2) but we might also envisage nucleophilic attack at the allylic position (S_N2'). At present there are no known methods for the preparation of such sulfamidates.



Scheme 58: Possible reactions of vinyl-substituted sulfamidates

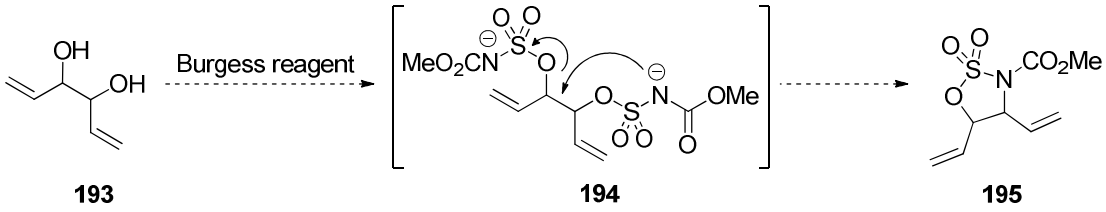
Nicolaou and co-workers have employed a double alcohol activation mechanism to form 1,2-cyclic sulfamidates from the corresponding 1,2-diols by utilising the Burgess reagent (Scheme 59).[73] The reaction is regioselective dependent on the substituents present.



Scheme 59: Nicolaou's route to sulfamidates derived from diols

2.1 Initial attempts at vinyl sulfamidate synthesis

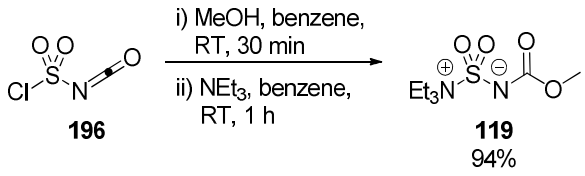
We initially investigated the synthesis of the 5-membered sulfamidate **195** (Scheme 60). By building upon Nicolaou's methodology we intended to prepare this highly functionalised sulfamidate, bearing two olefinic substituents, aiming to investigate its reactivity.



Scheme 60: Potential route to sulfamidate 195

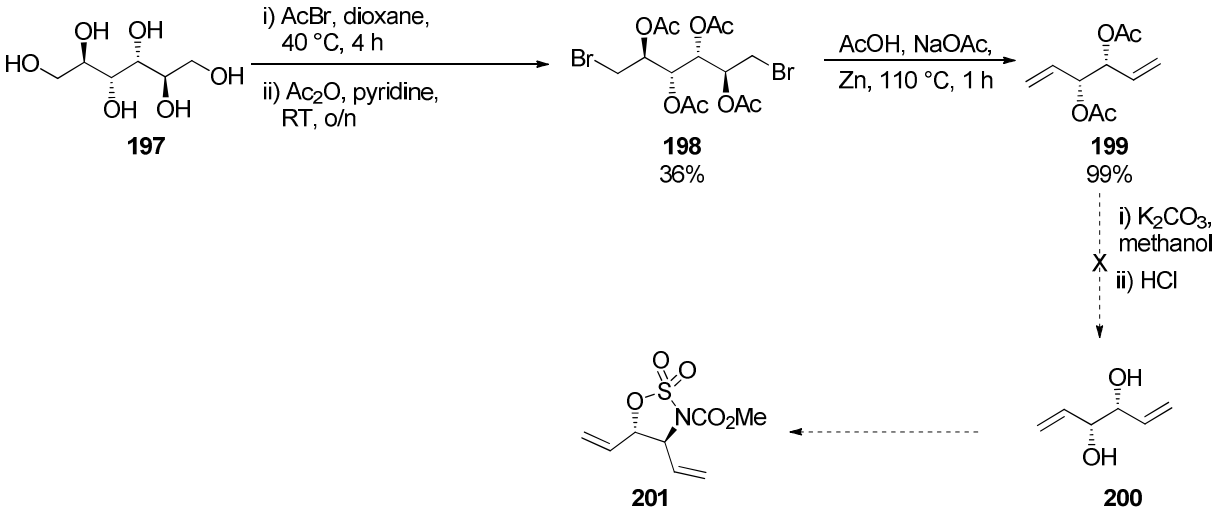
The preparation of Burgess reagent **119** was initially attempted using the conditions outlined by Burgess *et al.*, substituting benzene with toluene.[92] Chlorosulfonyl isocyanate **196** did not afford Burgess reagent when reacted as outlined in Scheme 61, with toluene as the solvent. When benzene was used the Burgess reagent was isolated in a 94% yield. Recrystallisation of Burgess reagent using hot toluene was also problematic and led to substantial decomposition of the desired material, therefore recrystallisation was

attempted at room temperature and at -78 °C which also led to considerable decomposition. The Burgess reagent also decomposed after 1 week in the freezer so it had to be used quickly once prepared.



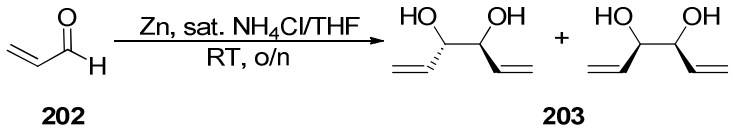
Scheme 61: Preparation of Burgess reagent 119

It was first envisaged that the sulfamidate **201** could be synthesised from the corresponding symmetrical diol **200** by treatment with 2 equivalents of Burgess reagent. A synthetic route to the diol **200** was undertaken starting from D-mannitol **197** (Scheme 62).[93] The primary alcohol groups were displaced with acetyl bromide followed by conversion of the secondary alcohol groups to the corresponding acetyl protected moieties giving **198**. Elimination of this more favourable leaving group afforded a crude mixture of the diene **199**. Attempted hydrolysis of the crude mixture followed by distillation led to decomposition. Attempts to reprepare **199** were relatively unsuccessful with mono-eliminated material being the main product from the reaction. It was decided that a new route to the diol **200** should be investigated.



Scheme 62: Potential route to sulfamidate 201 *via* diol 200

Acrolein **202** was reacted in the presence of zinc in attempts to prepare the racemic diol mixture **203** outlined in Scheme 63, using reaction conditions employed by Trost *et al.*[94] The crude reaction mixture did not look promising and it was noted that Trost *et al.* reacted this crude material further. It was envisaged that a clean sample of the diol would be required in order to investigate reactivity with the Burgess reagent and difficulties in purification led to isolation attempts being terminated.

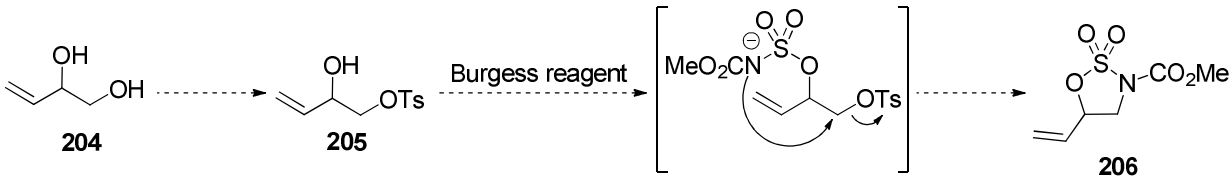


202 **203**

Scheme 63: Preparation of the racemic diol mixture 203

2.2 Initial investigations in regioselectivity switching

We next theorised that we could promote formation of the normally less favourable sulfamidate **206** by the prior introduction of a leaving group (Scheme 64). Initially the primary alcohol group would be converted to a leaving group to give **205** and then we supposed that the secondary alcohol group would react with the Burgess reagent and displace the pre-existing leaving group. This method would be used to overcome the natural substrate-controlled regioselectivity observed by Nicolaou.

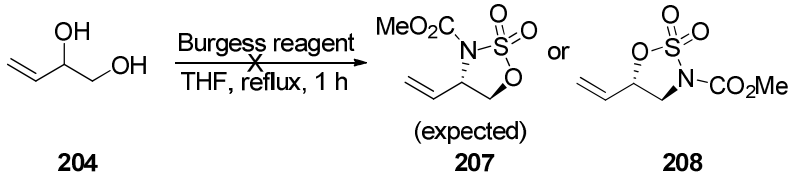


204 **205** **206**

Scheme 64: Potential route to regioselective sulfamidate formation

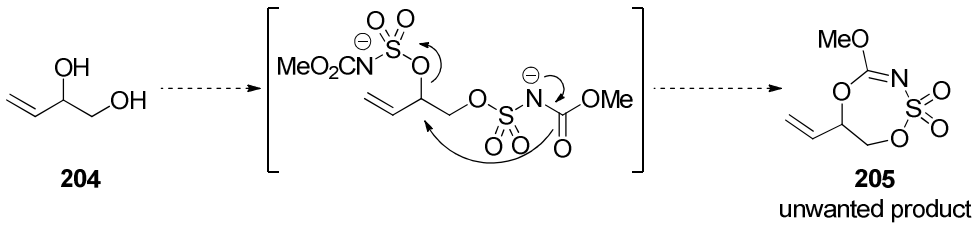
Further efforts to prepare sulfamidates with unsaturated substituents were investigated. Commercially available, 3,4-dihydroxy-1-butene **204** was reacted in the presence of Burgess reagent (Scheme 65).[73]

We investigated the reaction of diol **204** with 2.5 equivalents of Burgess reagent as a control. It was expected that depending on the more reactive alcohol we would see formation favouring one of the two possible products **207** or **208** outlined in Scheme 65. With a phenyl substituent Nicolaou recorded a 92% yield (93:7 ratio of regioisomers). The starting material **204** was consumed when refluxed for 1 h in the presence of the Burgess reagent with no sign of product by NMR.



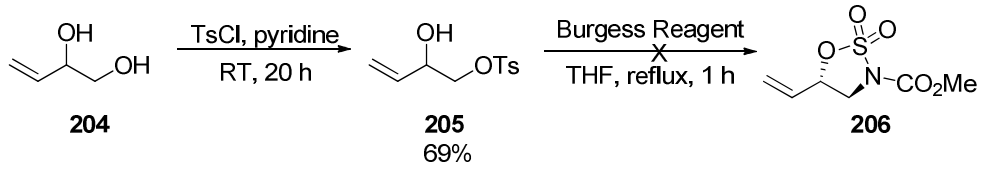
Scheme 65: Possible sulfamidates formed from reaction of diol 204 with Burgess reagent

The reaction was repeated at room temperature and after 30 minutes starting material was observed by TLC. The reaction mixture was stirred for a further 75 minutes and consumption of starting material was observed. Purification by column chromatography led to the isolation of a small amount of material which did not appear to be the desired product. It is possible that the activated alcohol group underwent an S_N2 reaction to afford the 7-membered ring **205** shown in Scheme 66. A similar by-product was evidenced by Metcalf when reacting diols bearing aromatic substituents in the presence of Burgess reagent.[95] It is also possible that this intermediate could undergo intermolecular polymerisation reactions that could account for the low mass recovery from column chromatography.



Scheme 66: Possible side reaction

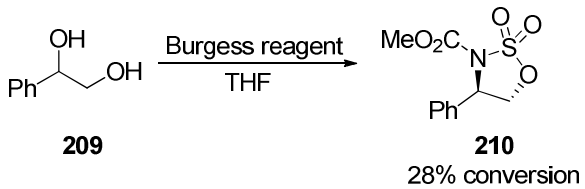
Monotosylation of 3,4-dihydroxybut-1-ene[96] **204** was next undertaken in order to investigate the possibility of forming sulfamidates by reacting tosylated alcohols with a slight excess of Burgess reagent (Scheme 67). When the tosylated alcohol **205** was reacted with Burgess reagent at room temperature the starting material was consumed after 2 hours. NMR analysis did indicate consumption of the starting material but again there was no evidence of product formation. We decided to reflux the reaction mixture in the hope that if an activated Burgess intermediate had formed that this would undergo reaction to the desired sulfamidate. Purification by column chromatography of the complex mixture was attempted, but was unsuccessful so we decided to refocus our endeavours.



204 **205** 69% **206**

Scheme 67:Attempts at switching regioselectivity in sulfamidate preparation

We decided to do a control reaction and attempted to prepare the known sulfamidate **210** using the same conditions as Nicolaou (Scheme 68).[73] Nicolaou obtained a 92% yield, we attempted this on a small scale and it appeared to have undergone 28% conversion to the desired material by NMR but was not reproducible when scaled up to 300mg.

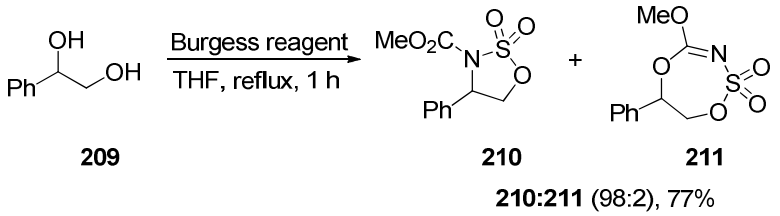


209 **210** 28% conversion

Scheme 68: Test reaction preparing a sulfamidate using Burgess reagent

Hudlicky *et al.* have shown that the half-life of the Burgess reagent is 19 minutes at reflux in tetrahydrofuran, with the reagent completely decomposing in less than 1 hour.[95] They also report a yield of 77% compared to a 92% yield reported by Nicolaou for the

transformation outlined in Scheme 68. Hudlicky observes the formation of the 7-membered by-product **211** also under these conditions (Scheme 69).

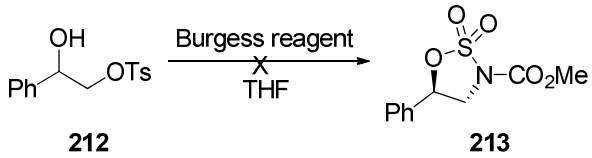


Scheme 69: Hudlicky's preparation of phenylated sulfamidate 210

Attempted scale up of this reaction was unsuccessful and so it was decided that we would investigate the possibility of simply switching regioselectivity rather than continue efforts into preparation of vinyl-substituted 5-membered sulfamidates.

2.3 More general attempts at regioselectivity switching

As Nicolaou *et al.* have shown that the phenylated 1,2-diol **209** reacts to give the sulfamidate **210** (Scheme 69) we decided to try and prepare the less favoured sulfamidate by attempting displacement of the tosylated diol to give the other sulfamidate regioisomer **213** (Scheme 70). This proved unsuccessful with consumption of starting material and no product formation.



Scheme 70: Attempts at switching substrate-biased regioselectivity in sulfamidate formation

The initial exploratory work outlined in this chapter, and the lack of success we encountered, led us to consider a different approach to the formation of cyclic sulfamidates and work was therefore focussed on metal-catalysed routes.

We therefore decided to investigate the possibility of preparing sulfamidates by possible gold(I)-catalysed hydroamination reactions and this work is outlined in Chapters 3 and 4 of this thesis.

Chapter 3

Preparation of Substrates for Allene Hydroamination

Chapter Three – Preparation of Substrates for Allene Hydroamination and Proof of Principle for gold(I)-catalysis

We were interested in testing the hypothesis that gold(I) could be used catalytically to form cyclic sulfamidates *via* a redox-neutral method, namely intramolecular hydroamination.

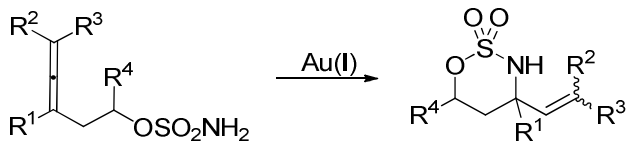


Figure 8: Hypothesis for Au(I)-catalysed sulfamidate formation

It was envisaged, by retrosynthetic analysis that the desired allenic sulfamates required for our investigations into gold-catalysed cyclic sulfamidate formation could be prepared from the corresponding allenic alcohol which could be accessed from Johnson-Claisen rearrangement of a suitably substituted propargyl alcohol, or alternatively from Crabbé homologation of homopropargyl alcohols (Figure 9).[97, 98] These two approaches give a wide range of substitution patterns.

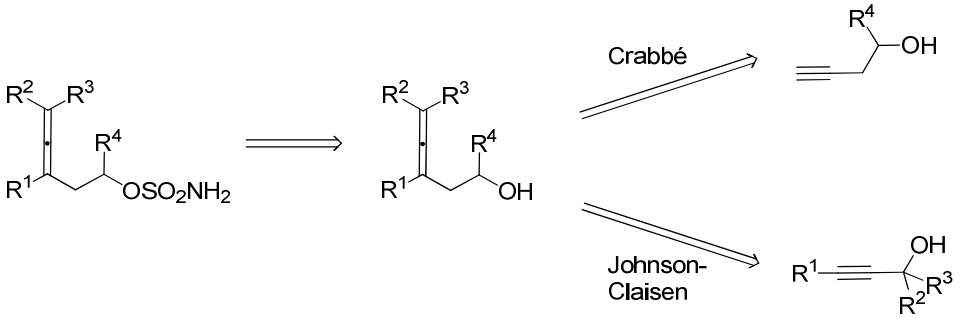
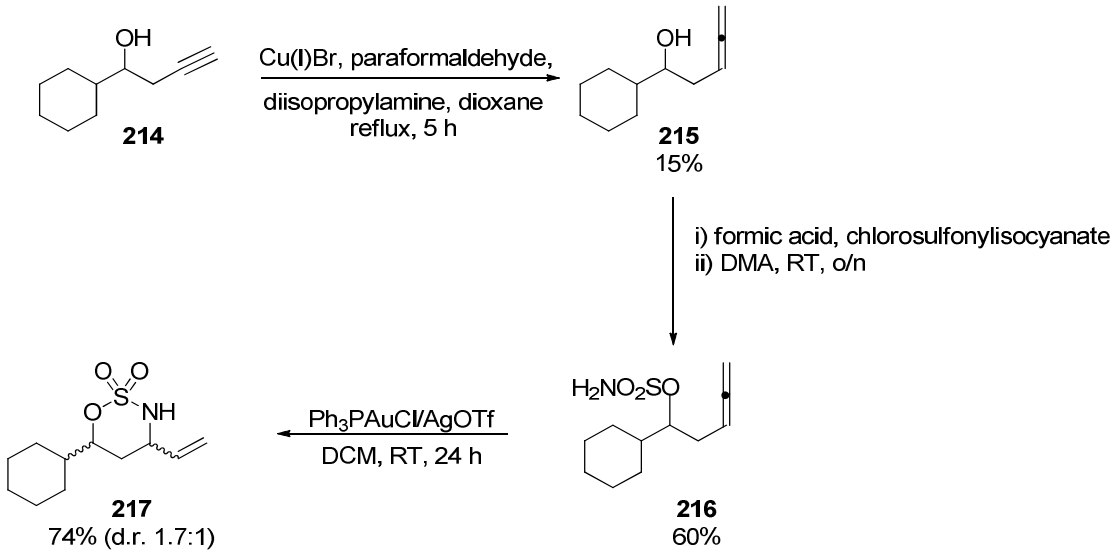


Figure 9: Retrosynthetic approaches to allenic sulfamates

We initially prepared the sulfamate **216** in order to test the gold methodology. The sulfamate was prepared from the corresponding allenic alcohol **215** via a Crabbé

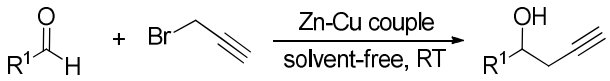
homologation. The allenic alcohol was prepared by a Barbier-type reaction from the homopropargyl alcohol **214** (Scheme 71). We were very pleased to find that the sulfamate did indeed give the cyclic sulfamidate **217**, in a 74% yield, when $PPh_3AuCl/AgOTf$ was used as a catalyst. With this promising result a range of sulfamates were prepared to test the scope of this reaction.



Scheme 71: Initial proof of concept

3.1 The Crabbé approach

3.1.1 Preparation of homopropargyl alcohols

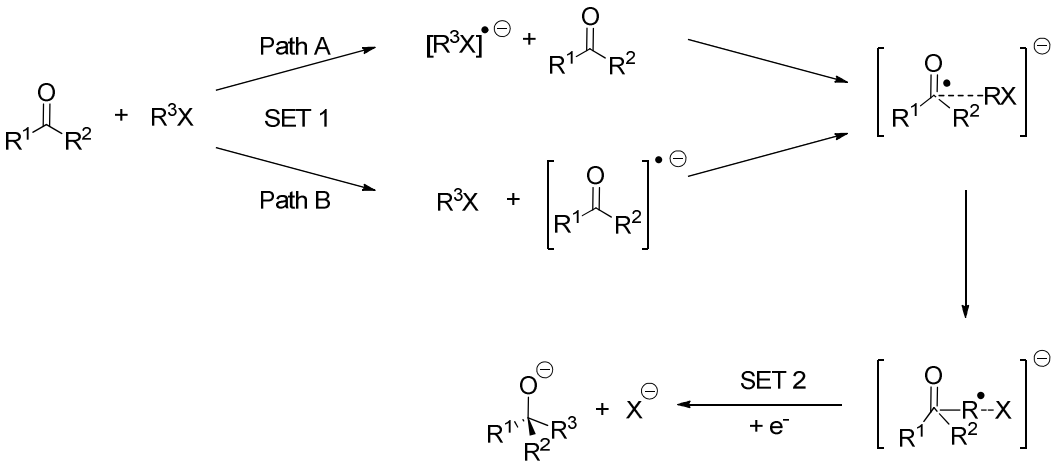


Scheme 72: Propargylation of aldehydes to give homopropargyl alcohols

In order to investigate the Crabbé homologation, we first needed a viable method for the preparation of homopropargyl alcohols. A range of homopropargyl alcohols were prepared utilising Barbier-type reaction conditions. The Barbier reaction is the reaction of an alkyl halide with a carbonyl group in the presence of a metal or a metallic salt

(Scheme 72).[99] Often confused with the Grignard reaction, but a crucial difference is that the Barbier involves *in situ* generation of the organometallic reagent in the presence of the electrophile, and in many cases proceeds in water.

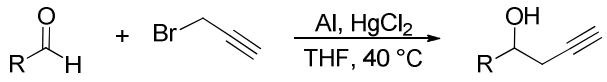
The Barbier reaction mechanism was investigated by Moyano *et al.*, showing that this reaction proceeds *via* radical intermediates.[100] Barbier reactions of unsaturated carbonyl compounds should involve firstly the formation of a carbonyl radical anion and proceed through path B (Scheme 73). If a saturated carbonyl compound undergoes reaction the initial step should be the formation of the halide radical anion (path A). The mechanism is easily predicted from the electron affinities of the reactants, with the radical anion being formed from the reactant with the highest electron affinity.



Scheme 73: Mechanism of the Barbier reaction

Ma has shown that aldehydes undergo reaction at room temperature with propargyl bromide in the presence of a Zn-Cu couple to give homopropargyl alcohols in excellent yields.[101] Zn-Cu couple was a favourable reagent due to the non-toxicity and low-cost. Unfortunately, when this reaction was attempted using *trans*-cinnamaldehyde we saw little conversion to the desired product. Ma achieved an 85% yield in the transformation utilising *trans*-cinnamaldehyde and we therefore concluded that the preparation of the Zn-Cu couple was ineffective. After a few attempts at this preparation it was decided to focus our efforts on a different Barbier-type reaction, employing aluminium as the metal.

When aluminium and mercuric chloride were employed we prepared cyclohexylbut-3-yn-1-ol **214** in a 88% yield (Table 1). *Trans*-cinnamaldehyde was transformed to the corresponding alcohol in a 87% yield.[102]



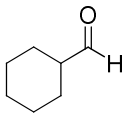
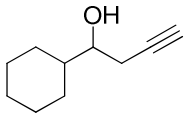
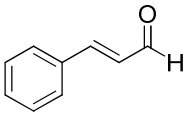
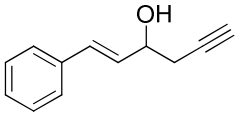
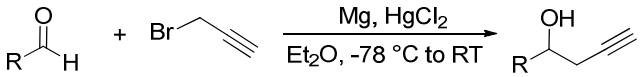
Starting material	Product	Yield
 **218**	 **214**	88%
 **219**	 **220**	87%

Table 1: Propargylation of aldehydes

Further Barbier-type reactions were undertaken using similar conditions but magnesium and mercuric chloride in diethyl ether were favoured as reagents as the start of the reaction could be observed clearly by the boiling of the diethyl ether solvent (Table 2).[103, 104]



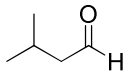
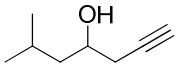
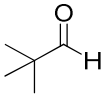
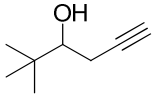
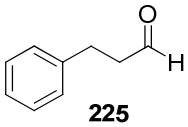
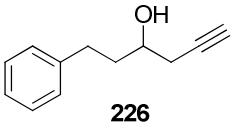
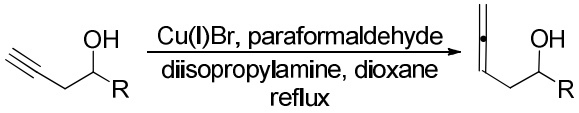
Starting material	Product	Yield
 **221**	 **222**	58%
 **223**	 **224**	33%
 **225**	 **226**	98%

Table 2: Propargylation of aldehydes using magnesium

Crabbé developed a one-step homologation of acetylenes to allenes with mild reaction conditions and good functional group tolerance (Scheme 74).[98] The use of copper bromide, paraformaldehyde and diisopropylamine as the reagents affords the desired transformation and is tolerant of alcohol, ether and ester groups (Scheme 74). This new method outlined by Crabbé is a clean and fast procedure and the lack of strong reducing agents is the key in functional group tolerance.



Scheme 74: Improved Crabbé homologation conditions

A range of allenes were synthesised to facilitate hydroamination studies. Allenes which did not bear substitutents at the terminal position were synthesised by the Crabbé homologation method (Table 3).

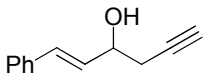
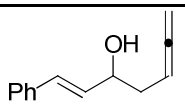
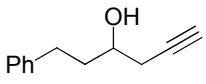
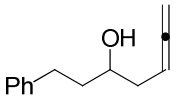
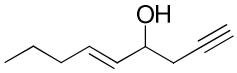
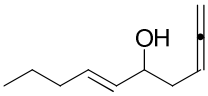
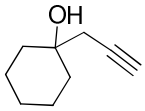
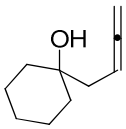
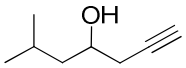
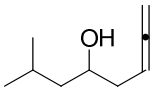
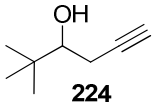
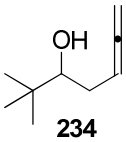
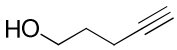
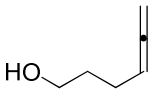
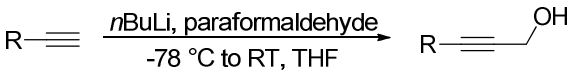
Starting material	Product	Yield
 **220**	 **227**	37%
 **226**	 **228**	48%
 **229**	 **230**	52%
 **231**	 **232**	33%
 **222**	 **233**	40%
 **224**	 **234**	42%
 **235**	 **236**	48%

Table 3: Allenes prepared by Crabbé homologation

3.2 The Johnson-Claisen approach

Another method employed for preparing acetylenic alcohols was by alkyne lithiation followed by subsequent reaction with paraformaldehyde.[105] 4-Methylpent-2-yn-1-ol **238** was the first alcohol prepared by this method (Table 4). This was achieved in a 96% yield (calculated by NMR) and reacted on crude. Other substrates were also prepared by this method (Table 4).



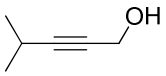
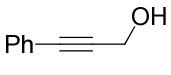
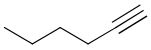
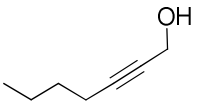
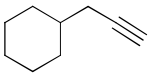
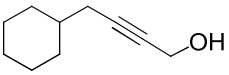
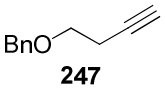
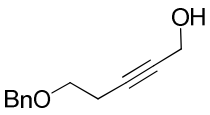
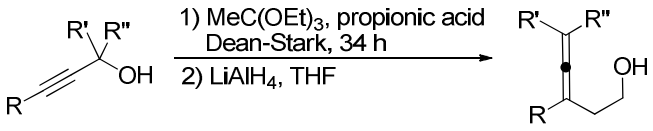
Starting material	Product	Yield
 **237**	 **238**	96%
 **239**	 **240**	73%
 **241**	 **242**	85%
 **245**	 **246**	86%
 **247**	 **248**	50%

Table 4: Preparation of acetylenic alcohols

A range of catalysts have been used in the Claisen rearrangement such as Lewis acids, Brønsted acids and bases.[106] For the preparation of allenic alcohols from terminally substituted propargyl alcohols we used propionic acid as the catalyst following methodology outlined by Ma (Table 5).[107]



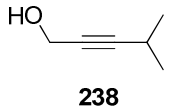
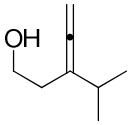
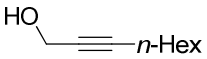
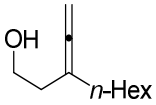
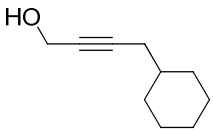
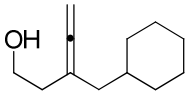
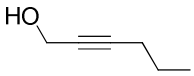
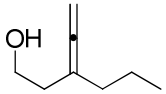
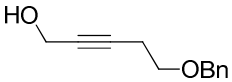
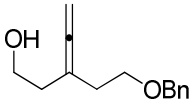
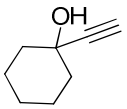
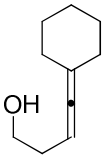
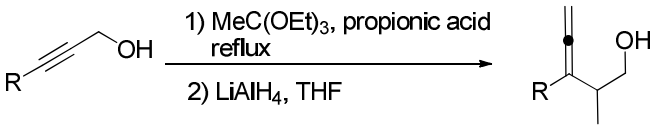
Starting material	Product	Yield
 **238**	 **249**	72%
 **250**	 **251**	38%
 **246**	 **252**	66%
 **253**	 **254**	40%
 **248**	 **255**	42%
 **256**	 **257**	21%

Table 5: Allenic alcohols from Claisen rearrangement

By replacing the triethylorthoacetate with triethylorthopropionate it was possible to introduce a methyl substituent as shown below (Table 6)[108] This was advantageous as it allowed for further investigation into substituent tolerance, with the methyl group being close to the reactive allene during the gold-catalysed sulfamidate formation.

The following methyl-substituted allenes were prepared to give a range of varying methyl-substituted sulfamidates. Aromatic and aliphatic functionality were both tolerated under these reaction conditions with similar yields achieved for all substrates.



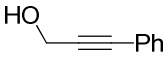
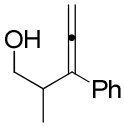
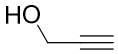
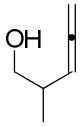
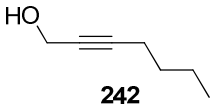
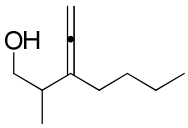
Starting material	Product	Yield
 **240**	 **258**	48%
 **259**	 **260**	47%
 **242**	 **261**	48%

Table 6: Methyl substituted allenic alcohols

With this range of allenic alcohols in hand we were then able to convert these to the desired sulfamates required to investigate the gold catalysis synthesis of cyclic sulfamidates.

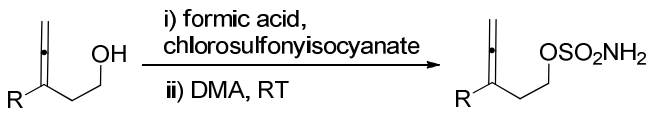
3.3 Sulfamate formation

Initial sulfamate formation was achieved by converting the corresponding alcohol to the sulfamate using conditions outlined by Okada *et al.*[109] Okada has shown that using DMA as a solvent accelerated the reaction compared to the solvents previously used in this reaction. DMF was shown to be a poor solvent choice for this reaction as DMF is involved in a side reaction with the sulfamoyl chloride and often the DMF adduct is

obtained ($^{-}O_3S$-^{+}NH=CH-NMe_2).[110] Previous sulfamoylation reactions were carried out in the presence of excess base but it was shown that by eliminating the base higher yields were obtained.

We synthesised a range of sulfamates with deca-3,4-dien-1-yl sulfamate **263** being prepared from the allenic alcohol **262** (Table 7). Sulfamoyl chloride (1.5 eq.) was formed *in situ* overnight and DMA was added. To this solution was then added the allenic alcohol **262** in DMA. This gave the desired sulfamate in a 62% yield.

Further sulfamates were prepared by reaction of the allenic alcohols with sulfamoyl chloride generated *in situ* with DMA as the solvent. The propyl substituted allenic alcohol **254** was converted to the sulfamate **264**. This provided a suitable precursor to probe the possibility of forming quaternary-centred sulfamidates which are known to be difficult to prepare by conventional sulfamidate methods known at this time. Other substituents were also introduced to diversify chain length such as the hexyl substituted sulfamate **265** and differing functional group tolerance with the preparation of the benzylated sulfamate **266**.



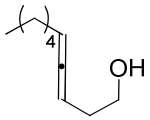
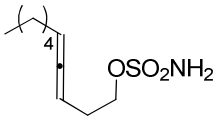
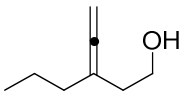
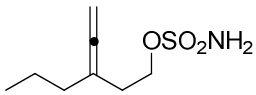
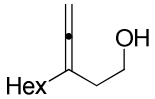
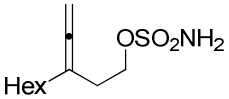
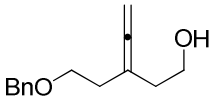
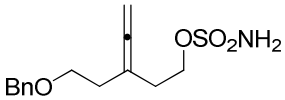
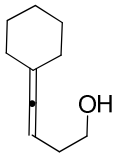
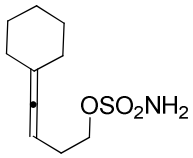
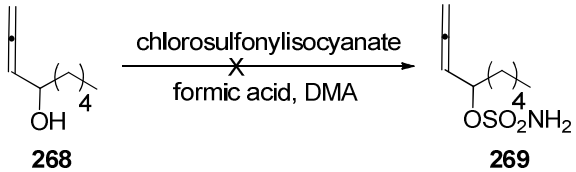
Starting material	Product	Yield
 **262**	 **263**	62%
 **254**	 **264**	43%
 **251**	 **265**	43%
 **255**	 **266**	45%
 **257**	 **267**	58%

Table 7: Sulfamate formation

The allenic alcohol **268** was the next substrate exposed to the sulfamoylation reaction conditions and this proved to be unsuccessful with several products observed by TLC (Scheme 75). In this case the hydroxyl group is *alpha* to the allene and this may be one of the factors leading to the formation of unwanted by-products.[79]



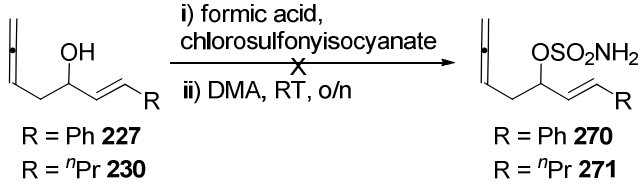
268 **269**

Scheme 75: Unsuccessful sulfamate formation

Kenworthy and Taylor[83] reacted homoallylic alcohols to give the corresponding sulfamate ester either by using the conditions outlined above or by using DCM as the solvent and pyridine (1.5 eq.) as a base. We employed pyridine as a base and DMA as the solvent in attempt to synthesise the desired sulfamate **269** but this was unsuccessful.

The reaction was attempted as above (Scheme 75) but the solvent changed to DCM. This showed mainly starting material after 5 hours. Further reaction conditions were investigated such as addition of pyridine to the reaction or pyridine and DMAP. All of the reactions had starting material present after 72 hours. Use of dichloromethane led also to the decomposition of the starting material.

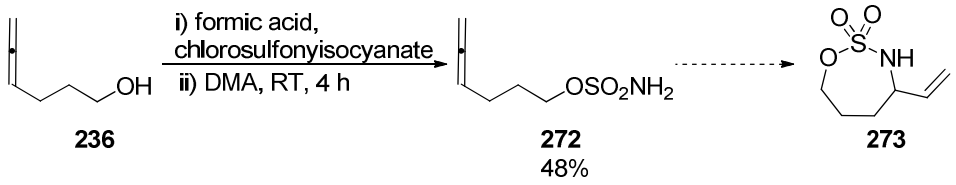
We decided to attempt the synthesis of the conjugated sulfamate **270** from *(E)*-1-phenylhepta-1,5,6-trien-3-ol **227** (Scheme 76). TLC analysis looked promising but when loaded onto a column the crude mixture turned brown. It appears that the product, if formed, is not stable as no sulfamate was isolated from purification by column chromatography.



Scheme 76: Attempts at formation of unsaturated sulfamates

We attempted to synthesise the sulfamate **271** to investigate the effect of a less conjugated starting alcohol **230**. The reaction mixture turned brown within one hour following the addition of the allenic alcohol, and starting material was consumed by TLC. NMR analysis of the crude reaction material showed no sign of product formation.

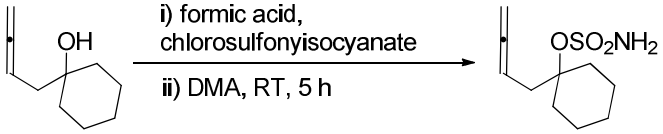
Investigation of larger sulfamidate ring sizes could be investigated by preparing hexa-4,5-dien-1-yl sulfamate **272** (Scheme 77). This was achieved in a moderate yield and will potentially provide a potential route to the 7-membered cyclic sulfamidate **273**.



236 **272** 48% **273**

Scheme 77: Sulfamate for 7-membered cyclic sulfamidate investigations

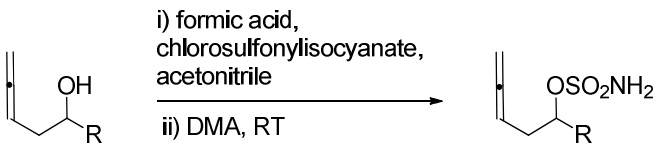
Diversity of sulfamates was further extended by the preparation of a sterically encumbered sulfamate (Scheme 78). This reaction gave a relatively low yield (29%) of the sulfamate but this may be due to the bulk around the alcohol group in the starting material.



232 **274** 29%

Scheme 78: Sterically restricted sulfamate formation

Further improvement on the sulfamoylation reaction conditions was sought at this stage.[111] Previously the sulfamoyl chloride was prepared neat and stirred overnight. The new reaction conditions are the same as above but acetonitrile was added to the neat sulfamoyl chloride solution and stirred overnight, leading to a dramatic increase in yield.[112, 113] Pyridine when added to one of the reactions with the allenic alcohol in DMA did not give any improvement.



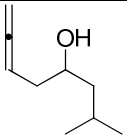
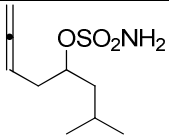
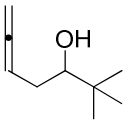
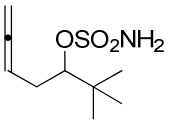
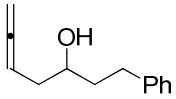
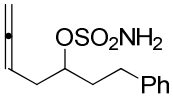
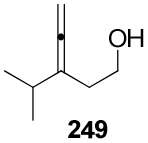
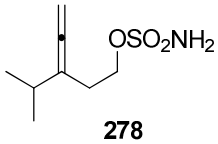
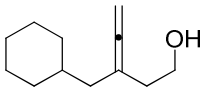
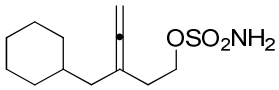
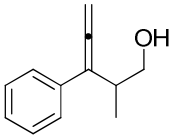
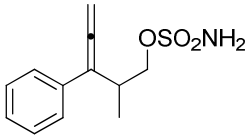
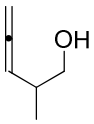
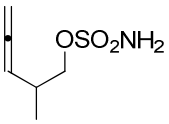
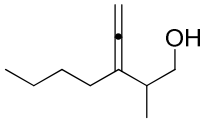
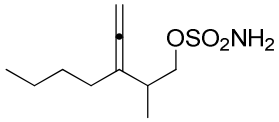
Starting material	Product	Yield
 **233**	 **275**	71%
 **234**	 **276**	41%
 **228**	 **277**	71%
 **249**	 **278**	54%
 **252**	 **279**	76%
 **258**	 **280**	65%
 **260**	 **281**	67%
 **261**	 **282**	78%

Table 8: Sulfamates prepared using optimised conditions

Further substitution was investigated with novel sulfamates being prepared by utilising the optimised reaction conditions (Table 8). Sulfamate **277** was prepared in order to test the tolerance of aromatic rings to our sulfamidate formations.

With the optimised conditions we revisited the preparation of precursors to quaternary centred sulfamidates synthesising the ^{i}Pr-substituted sulfamate **278** (Table 8) with a greatly improved yield compared to the ^{n}Pr-substituted sulfamate **264** which was isolated in a 51% yield (Table 7).

Preparation of a methylated sulfamate was also of interest to investigate the tolerance of substitution at the 2-position. The preparation of the 2-methyl substituted allenic sulfamates **280**, **281** and **282** added diversity to the potential sulfamidates that could be synthesised with a methyl group in the 2-position.

With this diverse range of sulfamates in hand, gold(I)-catalysed synthesis of cyclic sulfamidates could be investigated.

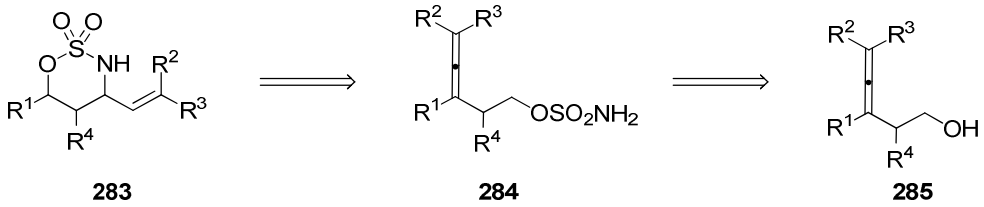
Chapter 4

Sulfamidate Synthesis by Gold(I)-Catalysed Hydroamination

Chapter Four - Sulfamidate synthesis by Au(I)-catalysed hydroamination - optimisation and controls

4.1 Initial investigations into gold(I)-catalysed hydroamination of allenes

We decided to investigate gold(I)-catalysis for the formation of cyclic sulfamidates from allenic alcohol precursors (Scheme 79). We initially investigated the use of the $PPh_3AuCl/AgOTf$ as the gold catalyst in the formation of sulfamidate **217** (Table 9).



Scheme 79: Retrosynthetic analysis of cyclic sulfamidates

We initially investigated the use of the $PPh_3AuCl/AgOTf$ as the gold catalyst in the formation of sulfamidate **217** and this was achieved in a 74% yield. We then carried out a catalyst screen to investigate the effect a change of catalyst would have on this reaction. Gagosz's complex **287** (PPh_3AuNTf_2) provided the highest yields (Table 9, overleaf).

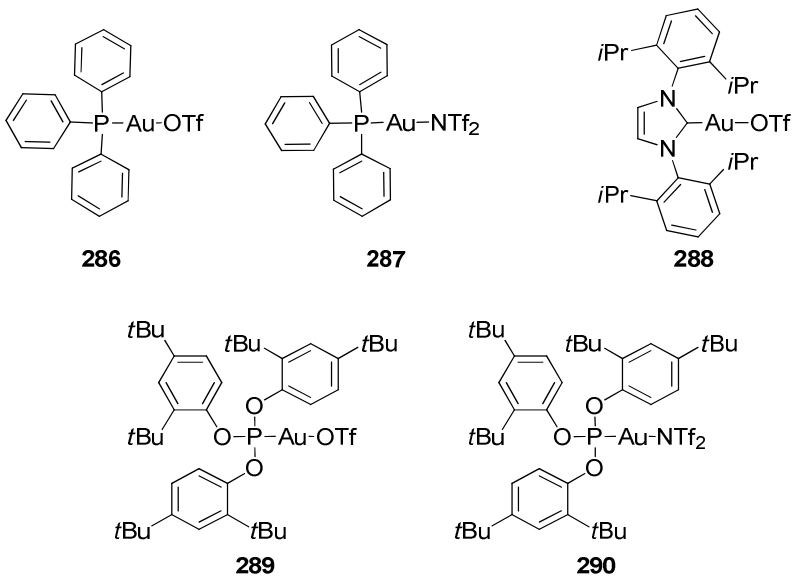
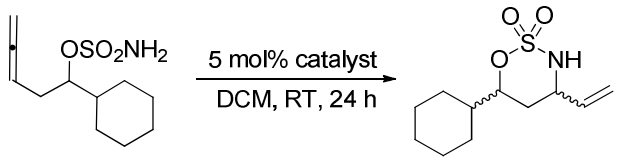


Figure 10: Catalyst Structures

We investigated a range of ligands on gold, such as the electron-rich carbene complex **288**, as well as the electron-poor phosphite complexes, ligands **289** and **290** (Figure 10). The yield was better in the case of the electron-poor ligand but it is not clear if this is solely due to the ligand being more weakly held by the gold or whether the bulk of the ligand may also play a part in the yields observed.

We altered ligands and various counterions which gave better diastereoselectivity in some cases, but to the detriment of the yield. Control experiments without any catalyst, with AgOTf only and with TfOH confirmed that the gold complex was necessary for reaction to occur (Table 9).



216 **217**

Entry	Catalyst	Yield 2/%	dr *cis/trans*
1	None	0	NA
2	AgOTf	0	NA
3	TfOH	0	NA
4	$(PPh_3)AuCl/AgOTf$ (**286**)	74	1.7 : 1
5	$(PPh_3)AuNTf_2$ (**287**)	99	1.2 : 1
6	IPrAuCl/AgOTf (**288**)	48	1 : 1
7	$(2,4\text{-Di-}t\text{BuPhO})_3PAuCl/AgOTf$ (**289**)	43	2 : 1
8	$(2,4\text{-Di-}t\text{BuPhO})_3PAuCl/AgNTf_2$ (**290**)	82	1 : 1

Table 9: Catalyst screen in the formation of 217

With the highest yields from the catalyst screen achieved with Gagosz's complex we decided to investigate the reactivity of other sulfamates in the presence of this catalyst. Sulfamidate **292** was formed as exclusively the *E*-alkene (Table 10). Substitution can be tolerated at the terminal position of the allene, with 4-cyclohexylidenebut-3-en-1-yl sulfamate **267** leading to the formation of sulfamidate **293** containing a trisubstituted

olefin. Secondary alcohols were reacted to afford sulfamates **275**, **276** and **277**, which gave mixtures of 1,3-*cis* and *trans* isomers with modest selectivity analogous to the diastereoselectivity observed in similar reactions.[77, 84, 114, 115]

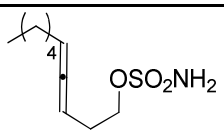
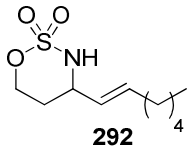
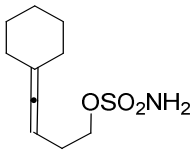
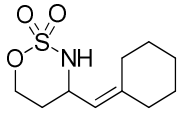
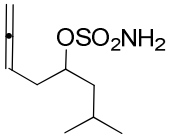
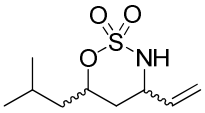
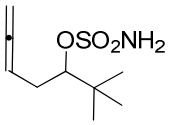
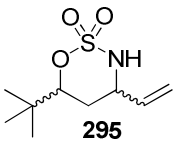
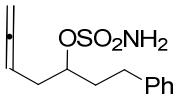
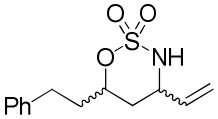
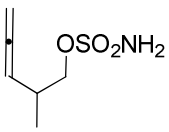
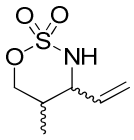
Entry	Sulfamate	Products	Yield
1	 **263**	 **292**	94%
2	 **267**	 **293**	66%
3	 **275**	 **294**	95% (1.8:1)
4	 **276**	 **295**	93% (2 :1)
5	 **277**	 **296**	95% (1.8 : 1)
6	 **281**	 **297**	75% (3 : 1)

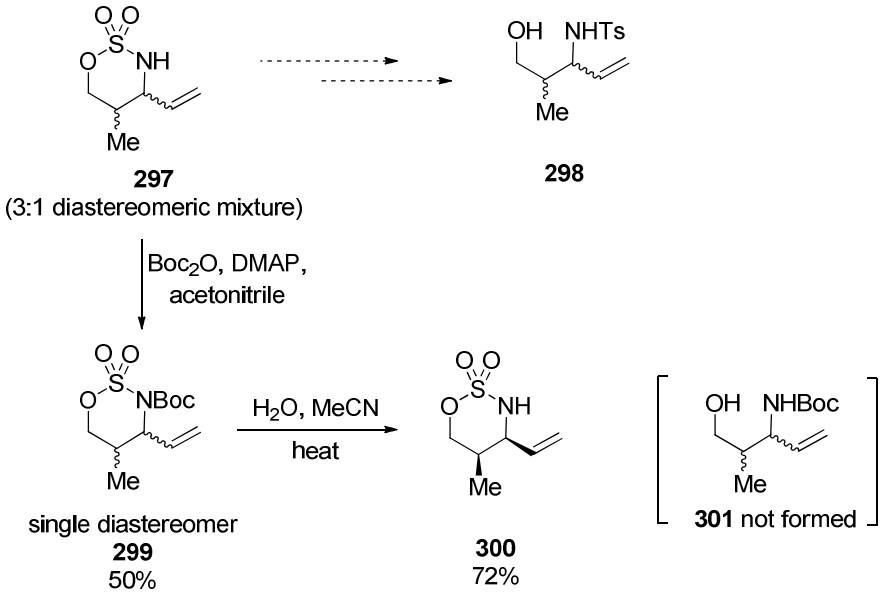
Table 10: Sulfamidates prepared

In the case of the sulfamidate **217** the diastereomers were separable and the major product was shown to be the 1,3-*cis* isomer (*cis*-**217**) by a single crystal X-ray diffraction study (Appendix A), the other 1,3-disubstituted products were assigned by analogy.

A control experiment, performed by subjecting the separable diastereomer *cis*-**217** to the original reaction conditions, showed that no equilibrium existed between the diastereomers. This is consistent with a kinetically-controlled cyclisation, which is common in other gold-catalysed hydroaminations.[116-118] The addition of protic additives (H_2O, AcOH, TfOH) to the reaction mixture did not accelerate the reaction to a measurable extent, suggesting that the final protonation is not the rate-determining step of this process.

The 2-substituted product **297** was formed as a 3:1 mixture of diastereomers and the relative stereochemistry of the major product could not be determined immediately. This was due to the C*H*NH overlapping with the N*H* signal in the ^{1}H NMR making it impossible to determine which isomer was more abundant from this data alone, due to an inability to observe the coupling constants.

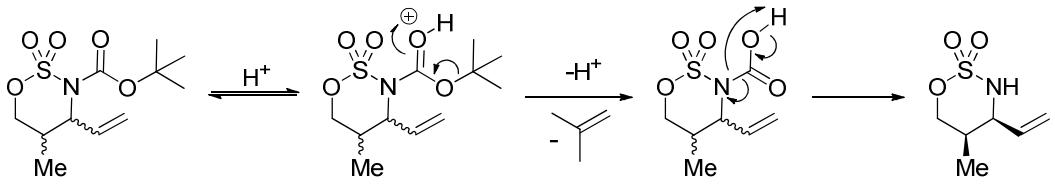
We therefore planned to convert the diastereomeric mixture into the corresponding known[119] *syn*- and *anti*- tosyl-protected amino alcohols **298** to elucidate the nature of the major product (Scheme 80). There were no examples of ring opening of unprotected sulfamidates so we decided to try a different protecting group (Boc) when tosylation failed.



Scheme 80: Determination of diastereoselectivity

However, we did not ultimately need to carry out this lengthy sequence in full. Boc-protection of the mixture **297** led unexpectedly to the isolation of a single diastereomeric product **299** in moderate yield.

We were once again unable to crystallise this compound, but attempted ring-opening using water in boiling acetonitrile leading only to slow loss of the Boc group (presumably by a thermal mechanism) (Scheme 81) to give a single diastereomer of **300**. Crystals suitable for an X-ray diffraction study were then obtained, revealing this product to be 2,3-*cis*-**300**. Comparison of the ^{1}H and ^{13}C NMR data with those obtained from the mixture arising from the gold-catalysed cyclisation confirmed that the *cis* diastereomer was indeed the original major product.



299 **300**

Scheme 81: Thermal mechanism for Boc-deprotection

Notably, the substitution patterns available are complementary to the work of Du Bois using Rh-nitrene chemistry of sulfamidates.[76] Du Bois has shown insertion into tertiary C-H bonds is faster than that into allylic and benzylic C-H bonds, and aziridination often predominates over allylic C-H insertion (Scheme 40, Chapter 1).

4.2 Preparation of *N*-quaternary-centred sulfamidates

We next decided to determine whether the reaction was suitable for the formation of *N*-substituted quaternary centres, since this is very rare for catalytic hydroaminations (*vide infra* Section 1.5.1, Chapter 1). This was successful with a range of *N*-substituted

quaternary sulfamidates **302**, **303**, **304** and **305** being synthesised in varying yields from the cyclisation of sulfamates **264**, **265**, **266 and 279** (Table 11).

When the steric bulk was increased at this quaternary centre we saw a reduction in yield and we reached the limits of the method in the case of substrate **278** (Table 11). This gave only a trace (~3%) of product **306** after 5 days at 40 °C. These unsaturated amine derivatives are difficult to access by other methods and have considerable potential for further functionalisation due to the presence of the olefinic group.

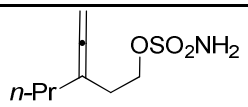
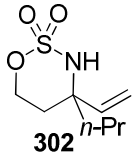
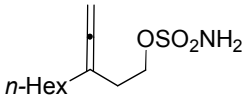
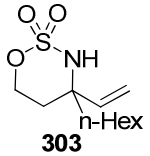
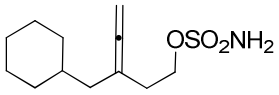
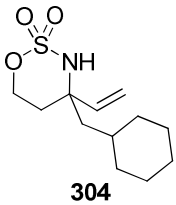
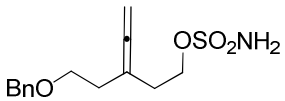
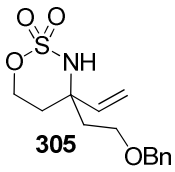
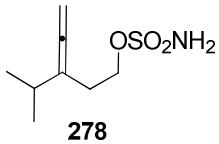
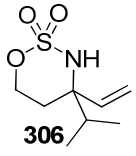
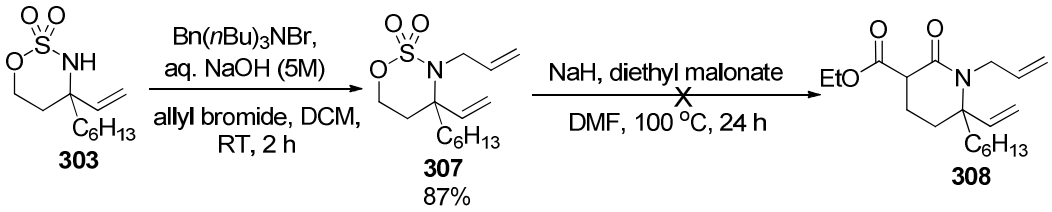
Entry	Sulfamate	Product[a]	Yield
1	 **264**	 **302**	92%
2	 **265**	 **303**	68%
3	 **279**	 **304**	37%
4	 **266**	 **305**	90%
5	 **278**	 **306**	Trace

Table 11: *N*-substituted quaternary sulfamidates

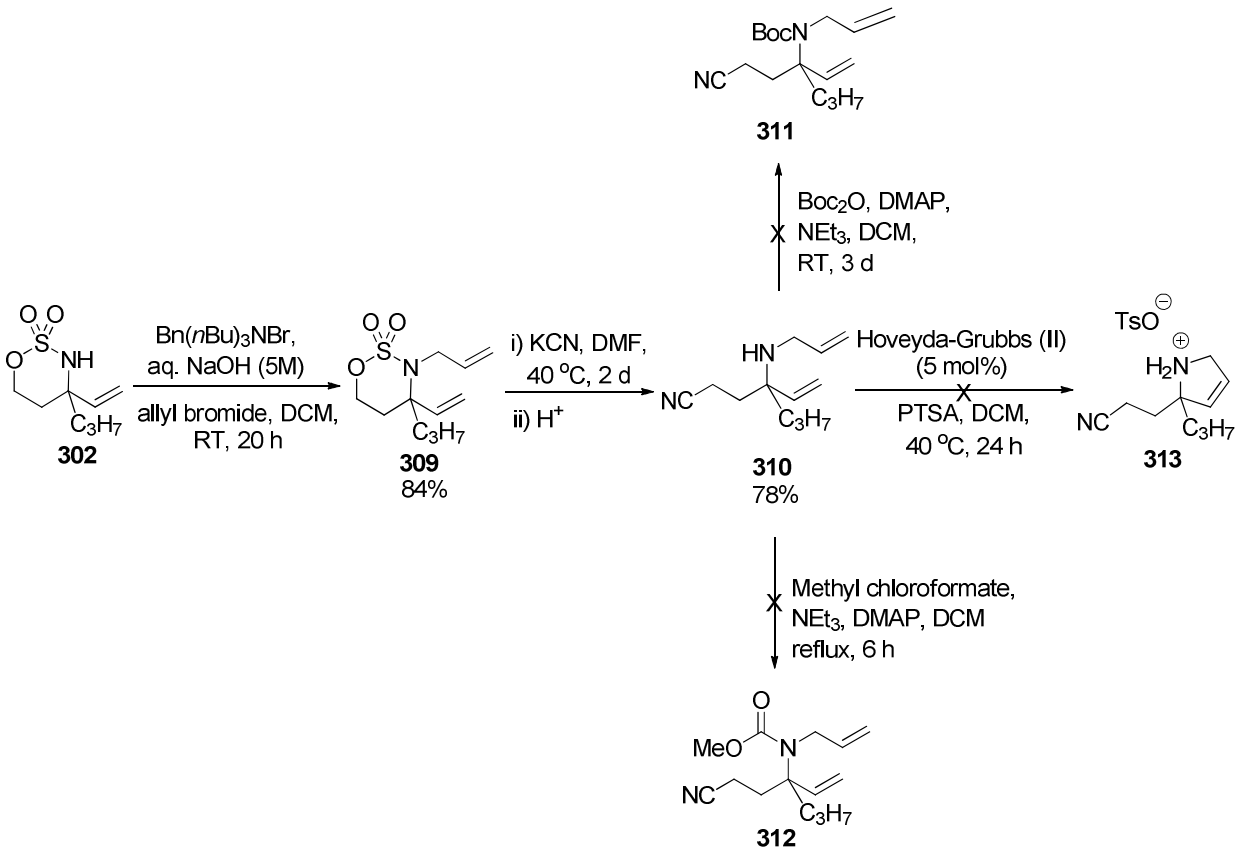
4.3 Sulfamidate reactivity

We decided to investigate the reactivity of the quaternary cyclic sulfamidates we had prepared. We initially attempted the preparation of piperidinone **308** from the allyl-protected sulfamidate **307** (Scheme 82). As this was unsuccessful we decided to focus on ring-opening of a quaternary sulfamidate instead.



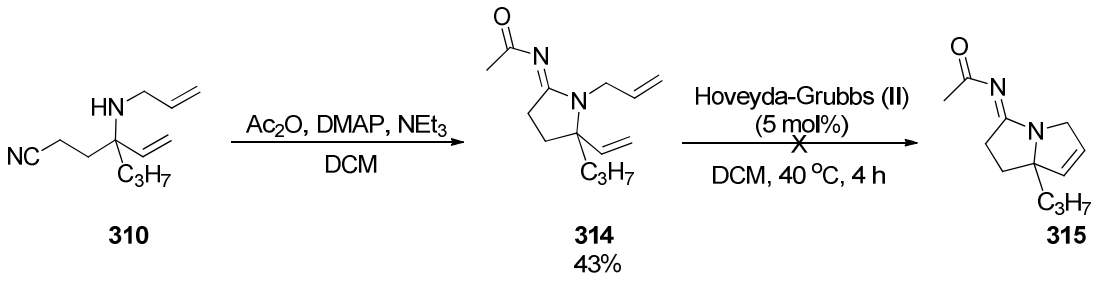
Scheme 82: Attempted piperidinone formation

Allylation of **302** to give **309** and ring-opening with cyanide ion occurred as expected to give the cyanoamine **310** after acid hydrolysis of the *N*-sulfate intermediate (Scheme 83, overleaf). We attempted to perform a ring closing metathesis reaction on **310** to give the cyclic amine **313** but no conversion was observed. We also attempted to protect the amine **310** to perform further transformations however the Boc-protection was unsuccessful. We attempted a further protection of **310** using methyl chloroformate and harsher conditions in an attempt to form **312** but to no avail.



Scheme 83: Attempted synthesis of cyclic amine 44

During our investigations into the reactivity of these sulfamidates, we did however discover unusual behaviour leading to a novel acyl amidine synthesis (Scheme 84). Standard acylation conditions of **310** did not give the expected acetamide, but a product ultimately identified as the amidine **314**. Presumably the intermolecular acylation of the amine is slow relative to its 5-*exo*-dig cyclisation onto the nitrile, giving a more nucleophilic amidine, which then undergoes acylation rapidly to give **314**. Related reactions are normally carried out in strong acid or base in two separate steps, rather than the relatively mild one-pot conditions found here.[120]

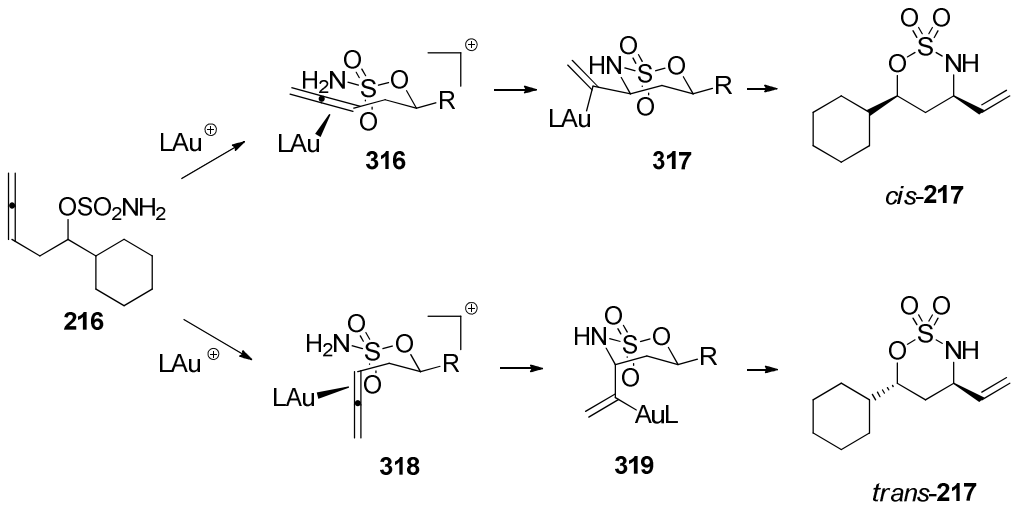


Scheme 84: An unusual acylamidine synthesis

4.4 Possible stereochemical rationale

Mechanistically, we anticipate that the reaction occurs *via* an outer sphere mechanism[121-126] leading to an *anti* aminoauration of the allene (Scheme 85). The *cis* and *trans* diastereomeric products may arise from the chair-like conformations **316** and **318** indicated.

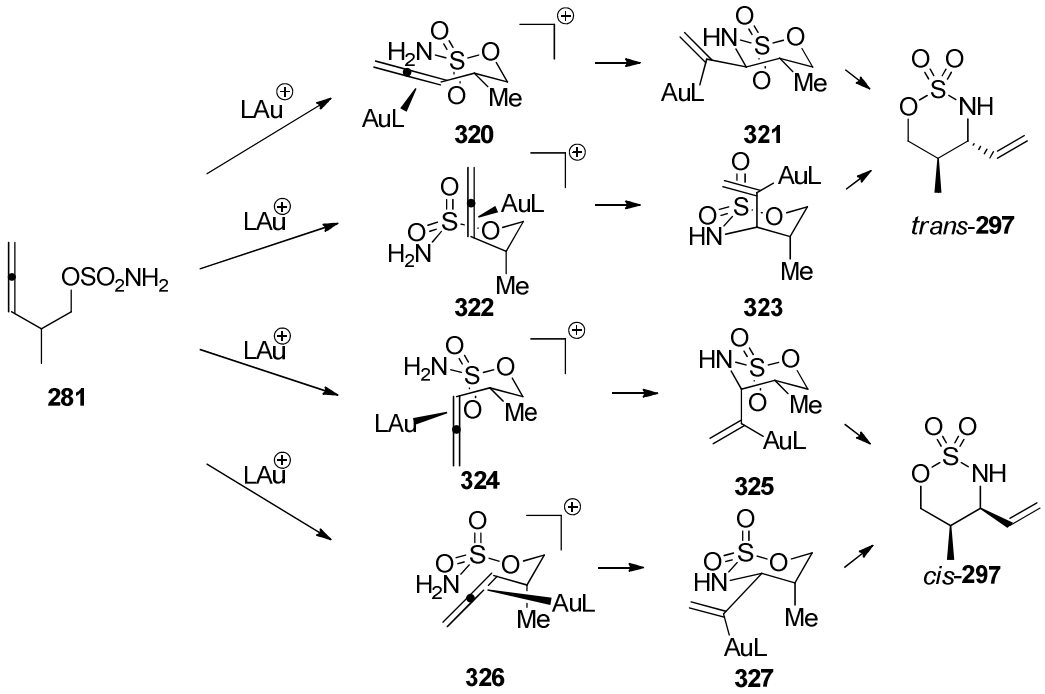
Protonation of the vinyl gold intermediates **317** and **319** would then give the observed products and regenerate the catalyst.



Scheme 85: Stereochemical rationale

The diastereoselectivity observed in the formation of **217**, **294**, **295** and **296** is lower than that normally found in related cyclisations, which is typically 4:1 to 7:1.[121] The explanation for this is currently unclear. At present, we postulate that **316** and **318** are in equilibrium[127] and that the observed diastereoselectivity for the *cis* products is due to faster and irreversible cyclisation of **316**, which has both the substituent R and the allene in equatorial positions. This would compare favourably with cyclisation of **318**, where the allene is in the axial position.

The observed diastereoselectivity in the formation of the 2-substituted system **297** was initially somewhat surprising and does not seem to have such a straightforward explanation. If the major product arose simply from a reactive conformation with the maximum possible number of equatorial substituents, then the major diastereomer would be expected to arise from conformation **320**, with both the gold-bound allene and the methyl group in equatorial positions (Scheme 86). This would lead to the preferential formation of the *trans* product, but we have demonstrated unequivocally that the major product is *cis*-**297**. Assuming a chair-like transition state, two reactive conformations leading to the *cis*-product are **324** and **326** leading to **325** and **327** respectively. There is no obvious reason why **324**, with the allene in the axial position, would be favoured over **320**, and indeed the steric bulk of the nearby substituent R is likely to clash with the metal-ligand assembly. Conformation **326** is thus probably more likely to be responsible for the formation of the major product - the gold-bound allene is equatorial, and although the group R is now axial, it is now less likely to interfere with the metal-allene binding. This would also be consistent with our analysis of the 1,3-disubstituted systems – the allene is equatorial in the suggested favoured conformation **316**, but substituent R is perhaps in this case sufficiently distant not to affect the metal-allene interaction when in the equatorial position. A fourth possible conformation of **281** that would give rise to *trans*-**297**, with *both* substituents in axial positions, **321**, was considered energetically unlikely.



Scheme 86: Stereochemical rationale for diastereoselectivity of sulfamidate 297

In summary, we have demonstrated the first gold-catalysed preparation of cyclic sulfamidates, leading to a range of substituted and sterically hindered products under mild conditions.

4.5 Unsuccessful substrates

When there is an unsaturated group on the oxygen bearing carbon, *e.g.* **271**, the sulfamate proved unstable to chromatographic purification attempts (Figure 11). ^{1}H NMR indicated sulfamoylation had occurred (new signal at 5.65 ppm corresponding to C*H*OSO_2NH_2). Sulfamates with bulky substituents such as **274**, **280** and **282** proved unsuccessful in forming the corresponding sulfamidates, this is likely due to steric hindrance. Formation of a 7-membered cyclic sulfamidate was attempted from sulfamate **272** but after several days no noticeable conversion was detected. Had we been able to prepare **269** we could have investigated the possibility of preparing sulfamidates with a smaller ring size but decomposition occurred rapidly upon subjecting the alcohol to the sulfamoylation conditions.

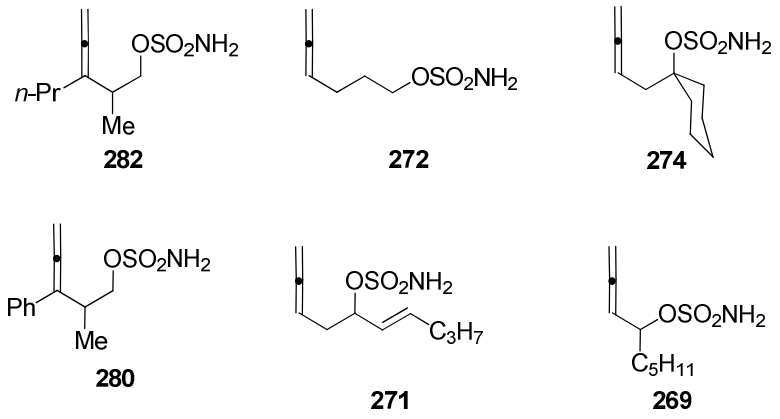
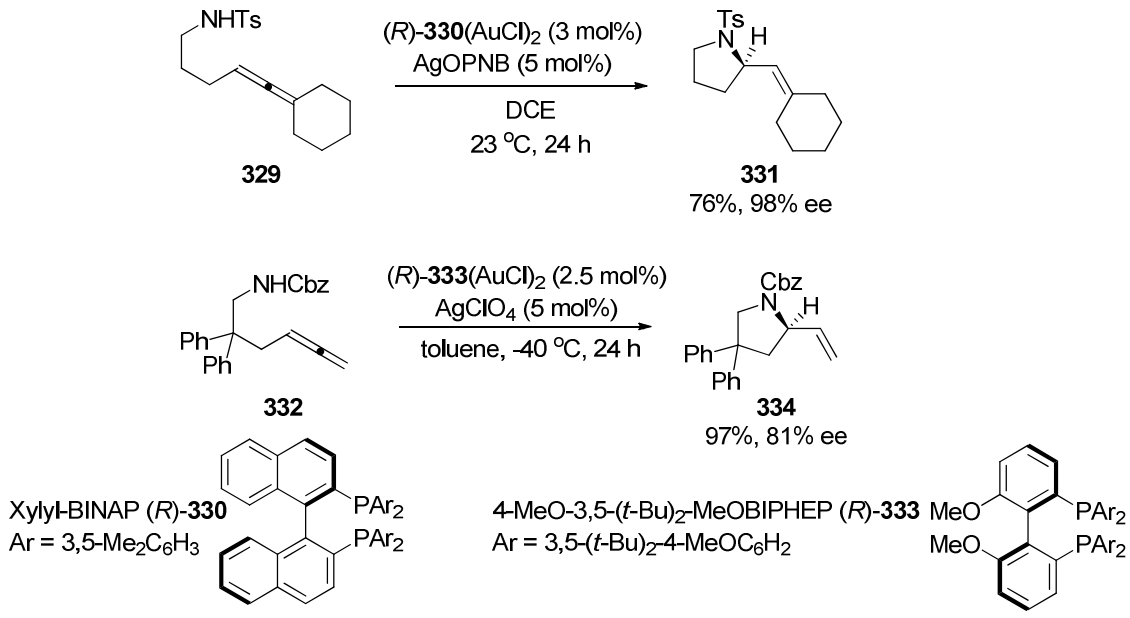


Figure 11: Unsuccessful sulfamate substrates

4.6 Future Work

The best success was noted in the forming of 6-membered sulfamidates. Initial forays at forming 5- and 7-membered sulfamidates were unsuccessful but with a little furtherth a little further investigation this may have been possible.

A general catalytic asymmetric approach to C-tertiary amines has so far proved elusive. Given our results, this new hydroamination reaction has the potential to address this important problem. It is known that for gold(I) complexes the chiral information imparted by the two electron donor ligand is at 180° from the potential reacting centre. Impressive levels of enantioselectivity have been obtained with similar substrates[128-130] such as in the formation of **331** as outlined by Toste and coworkers using digold complexes (Scheme 87).[131] By exploring the use of chiral gold ligands, digold complexes or counterions it may be possible to prepare enantioselective cyclic sulfamidates from the corresponding allenes.



Scheme 87: Enantioselective cyclisation of δ-allenyl sulfonamide to corresponding pyrrolidines

Chapter 5

Earlier Work: Attempts to Prepare a Thermally Unmasked Acyl Anion Equivalent

Chapter 5: Earlier work: Attempts to Prepare a Thermally Unmasked Acyl Anion Equivalent

This work was undertaken at the beginning of my doctoral studies with the aim of producing a novel acyl anion equivalent. This chapter provides an introduction to this field and outlines the efforts undertaken to synthesis a novel acyl anion equivalent.

5.1 Acyl Anion Equivalent Methodology

The stereoselective preparation of 1,n-dioxygenated compounds (n=2-6) is of vital importance in synthesis.[132] Versatile reagents were sought to facilitate preparation of a variety of compounds which would form building blocks for natural products and pharmaceuticals. It was thought to be of great importance to develop reagents that would permit catalytic asymmetric synthesis and multiple one-pot bond-forming reactions which would allow the rapid preparation of complex molecular frameworks.

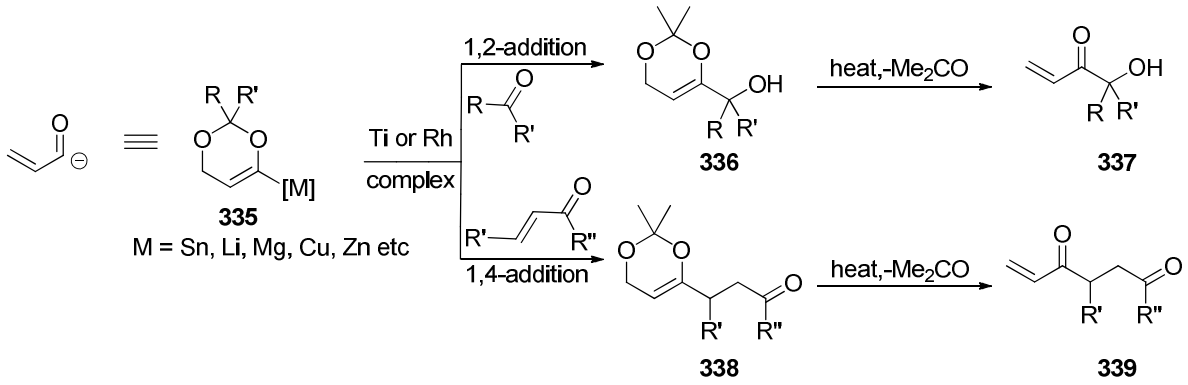
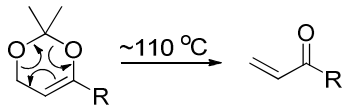


Figure 12: An α,β-unsaturated acyl anion equivalent

The development of the substituted dioxin **335** (Figure 12) would have given rise to an acyl anion equivalent which would have permitted the catalytic asymmetric synthesis of 1,2- and 1,4- deoxygenated compounds. It is possible to facilitate the 1,2- and 1,4- asymmetric additions to enones. Walsh[133] and Hayashi[134, 135] have developed catalytic

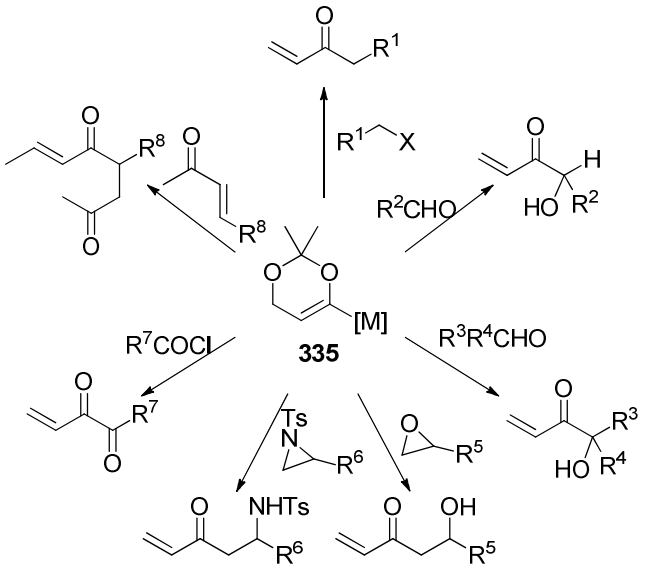
systems to catalyse the asymmetric additions of sp^2-hybridised nucleophiles to ketones. We envisaged using this chemistry to perform similar reactions with our proposed metallated dioxin **335**.

The dioxin would subsequently have been converted to the carbonyl derivative by a thermally-induced retro-Diels-Alder reaction[132] (Scheme 88), therefore facilitating multiple one-pot C-C bond forming reactions.



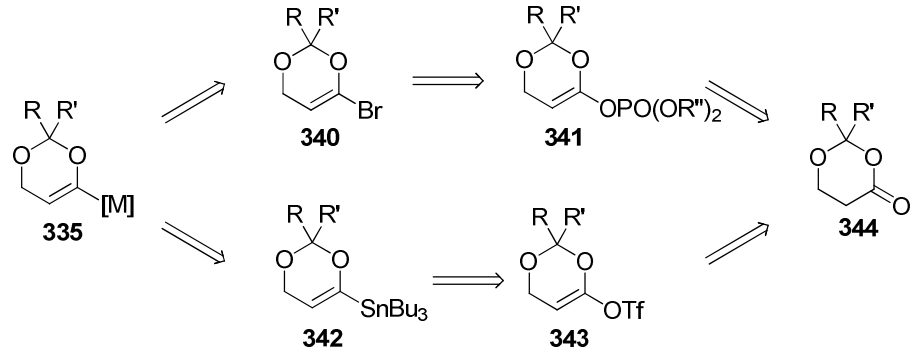
Scheme 88: Thermally-induced retro-Diels-Alder reaction

It was envisaged that dioxin **335** would undergo reaction with a broad range of electrophiles as outlined in Scheme 89 giving rise to an array of possible products once unmasked.



Scheme 89: Examples of possible electrophilic trapping with dioxin 335

The generalised target organometallic dioxin **335** was proposed to be synthesised from the corresponding lactone **344** (Scheme 90). We thought that dioxin **335** would come from a lithium-halogen exchange with bromide **340** or a lithium-tin exchange from the stannane **342**. The stannane **342** would be generated from the corresponding triflate **343** afforded from the lactone **344**, whilst the bromide **340** could be derived from the phosphonate ester **341** which in turn could be generated from the lactone **344**. This strategy was designed to ensure low temperature α-metallation.



Scheme 90: Retrosynthetic analysis of metallated dioxin 335

At present many α,β-unsaturated acyl anion equivalents have low regioselectivity of electrophilic attack and require acidic conditions for the hydrolysis step. This limits further reactivity in the same vessel and would affect acid sensitive groups that may be present in the complex target molecules. Some masked unsaturated acyl anion equivalents have already been synthesised based on metallated allenyl ethers or thioethers (Figure 13).[136]

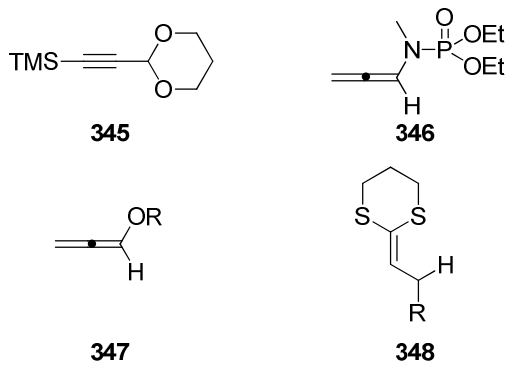
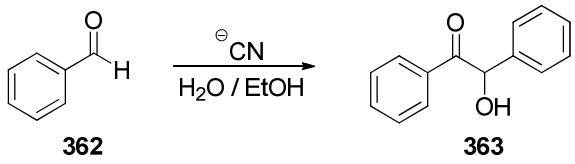


Figure 13: Examples of synthetic equivalents for acyl anion equivalent 335

5.2 Current approaches to the preparation of acyl anion equivalents

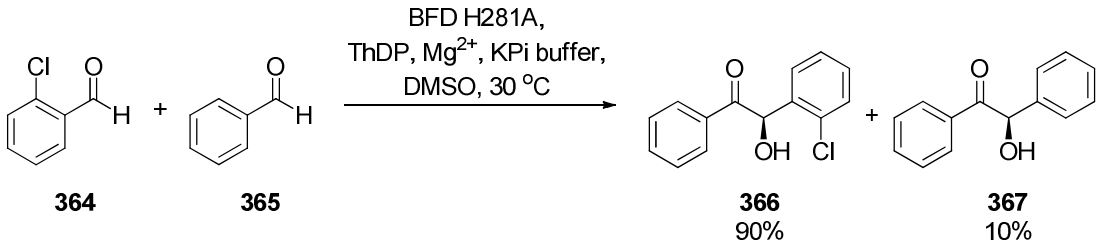
The use of reagents that are able to reverse their functional polarity is an area of continuing interest and has great potential applications allowing unusual disconnection strategies. These reagents are known as umpolung reagents and were given the name by German chemist Dieter Seebach.[137]

The benzoin condensation has been known for over one hundred years and is one of the most direct methods of producing an umpolung reagent.[138] Initially only aromatic aldehydes could be coupled to afford α-hydroxyketones (Scheme 91). Attack of a cyanide ion gives rise to a cyanohydrin intermediate which after deprotonation leads to the conversion of the originally electrophilic carbon to a nucleophilic centre.



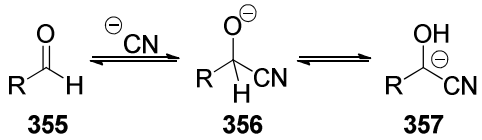
Scheme 91: Benzoin condensation

Major advances have been made in the last decade with Müller and co-workers developing the first cross-benzoin condensation (Scheme 92).[139]



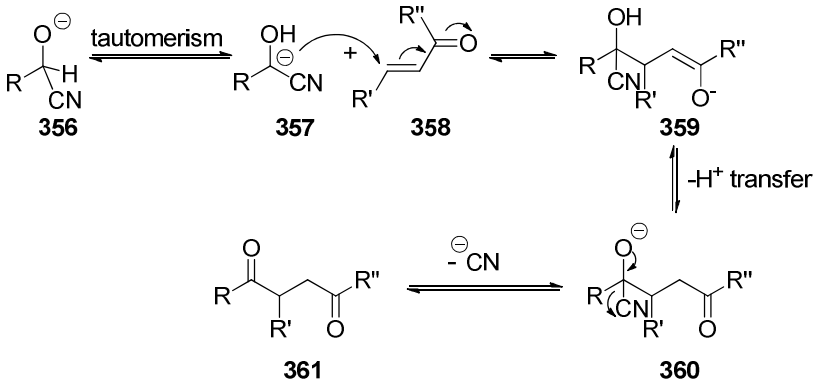
Scheme 92: Cross-benzoin condensation

This makes it possible to predict the preferred product for a given pair of aldehydes. Aromatic aldehydes reacted in the presence of an enzyme catalyst giving rise to high regioselectivity and enantio-enriched products.



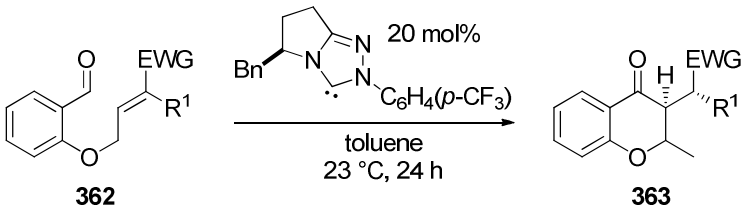
Scheme 93: Formation of umpolung reagent

The umpolung reagent formed in Scheme 93 reacts in the Stetter reaction. The Stetter reaction is a 1,4 conjugate addition of an aldehyde to an α,β-unsaturated compound which is catalysed by cyanide or a thiazolium salt (Scheme 94).[140] The Stetter reaction competes with the benzoin reaction outlined above which leads to the corresponding 1,2-addition. As the benzoin side reaction is reversible the main product from the Stetter reaction will be the 1,4-addition product which is the thermodynamic product. The above nucleophile **357** is generated *in situ* and reacts with an α,β-unsaturated compound to give the desired product.



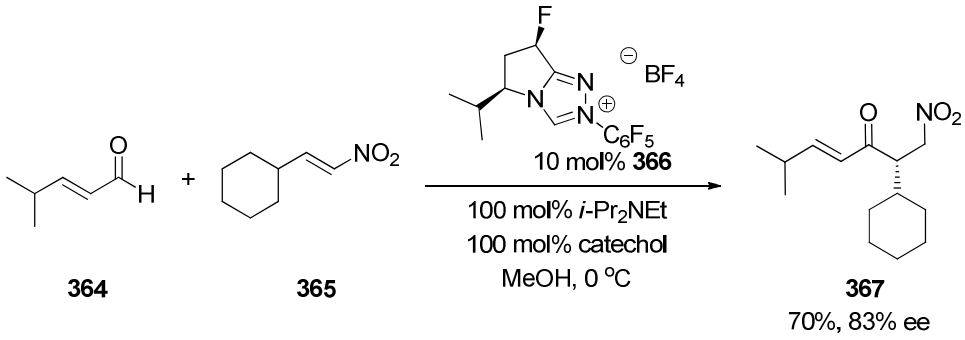
Scheme 94: Mechanism of the Stetter reaction

In recent years the asymmetric conjugate addition of nucleophiles to α,β-unsaturated carbonyl compounds has advanced with interest in tandem reactions coming to the fore.[141] By trapping the anionic intermediate formed it is possible to form two contiguous stereocentres. Rovis *et al*. have carried out highly enantio- and diastereoselective intramolecular Stetter reactions as shown in Scheme 95.[142]



Scheme 95: Enantio- and diastereoselective intramolecular Stetter reaction

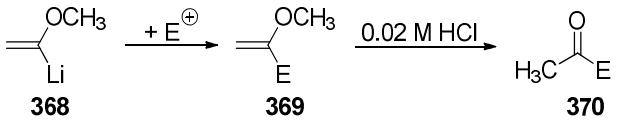
Recently Rovis *et al.* have demonstrated that intermolecular Stetter reactions of unsaturated aldehydes can be achieved using N-heterocyclic carbenes as catalysts.[143] This can be achieved in high yields and with good enantioselectivity using the thiazolium salt **366** as a precatalyst (Scheme 96).



Scheme 96: Intermolecular Stetter reaction of unsaturated aldehydes

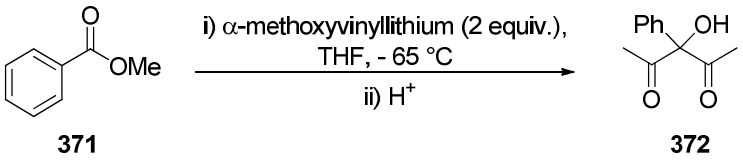
5.2.1 Use of Metallated Enol Ethers

Metallated enol ethers have been known since 1951.[144] Schöllkopf[145] and Baldwin[146] were the first to realise the potential of these compounds as acyl anion equivalents. Baldwin discovered that α-methoxyvinyllithium species were attractive substrates for use as acyl anion equivalents. The reaction of α-methoxyvinyllithium species with an electrophile gives rise to a product containing a vinyl ether (Scheme 97). This can easily be converted to the carbonyl compound by treatment with aqueous methanolic 0.02M HCl. This acyl anion equivalent will react with many different electrophilic substrates. Reaction with aldehydes and ketones affords hydroxy enol ethers and α-ketols. Steric bulk is also tolerated with reaction of hindered carbonyl groups such as keto-steroids.[146]



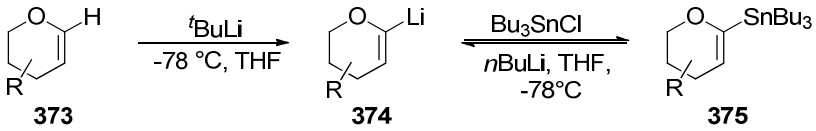
Scheme 97: α-Methoxyvinyllithium as an acetyl anion equivalent

It is also possible to synthesise dicarbonyl compounds from reaction of an α-methoxyvinyllithium species with nitriles. If an ester undergoes reaction with 2 equivalents of α-methyoxyvinyllithium species this provides high yields of substituted hydroxypentanediones **372** (Scheme 98). It was noted by Baldwin that exclusively 1,2-addition with α,β-unsaturated systems occurs with no conjugate addition found.[147]



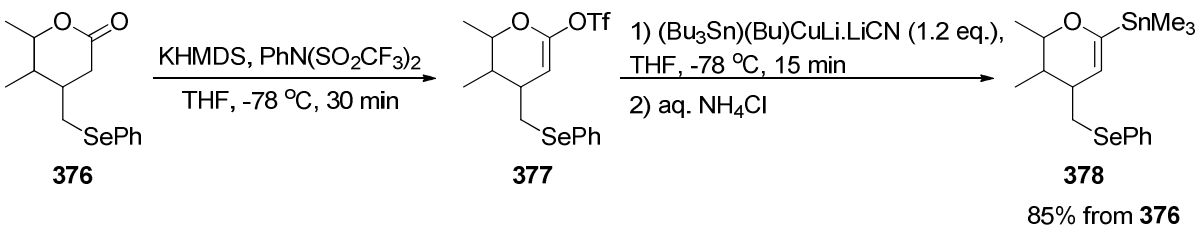
Scheme 98: Synthesis of hydroxypentanediones

It is accepted that the best approach for metallation of an enol ether is by reaction with *t*-butyl lithium in tetrahydrofuran at -78 °C (Scheme 99).[148] 2-4 equivalents of *t*-butyl lithium are required as dependent on substitution more equivalents may be required to give quantitative conversion to the vinyl anion. In order to overcome problems associated with the presence of excess *t*-butyl lithium the α-lithiated enol ether can be converted to a stannane which undergoes rapid Li-Sn exchange at low temperature.[149] This can be purified by chromatography and undergo transmetallation with *n*-butyl lithium to give the desired α-lithiated enol ether.



Scheme 99: Formation of the stannane from the enol ether

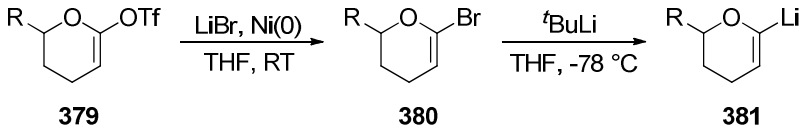
Another method for the formation of stannanes is to proceed *via* a triflate *e.g.* **377** which can undergo a copper-mediated coupling to give the desired stannane **378**.[150]



Scheme 100: Copper-mediated coupling to give the desired stannane

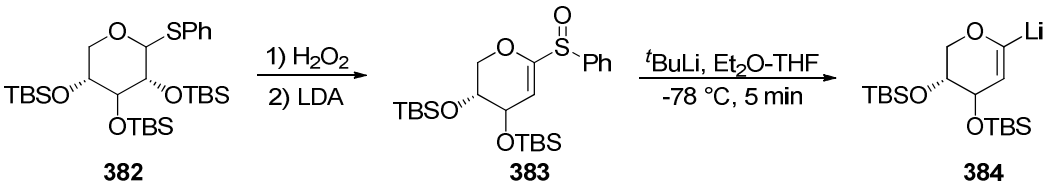
Before this could only be achieved by the reaction of the enol triflates with $Me_3SnSnMe_3$ in a Stille-type coupling but the tin reagent is very expensive and toxic. The reaction does not facilitate the formation of five membered enol ethers.[151] The Stille-type reaction gives a volatile tin by-product that is also extremely hazardous.

Another alternative way to form an α-lithio enol ether is *via* the α-brominated enol ether (Scheme 101). Yu and Lin have demonstrated the addition of HBr to alkynol ethers however, this does not work for cyclic systems.[152] Kocienski has shown that it is possible to use Ni to catalyse the coupling of LiBr to give α-brominated compounds which can subsequently be transformed to the corresponding lithium derivative.[153] The disadvantage here is the instability of the α-bromo enol ethers.



Scheme 101: Triflate to lithiated enol conversion

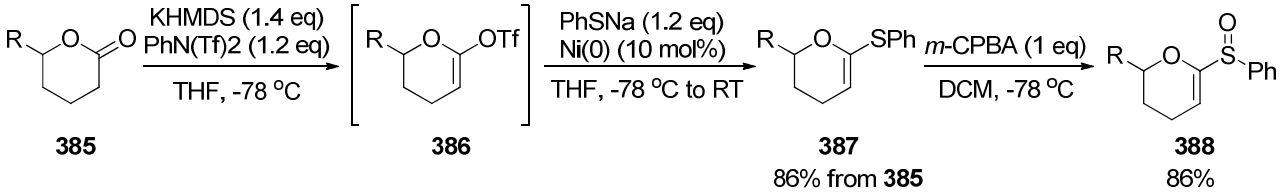
Kocienski has also shown that sulfoxide-lithium exchange is another possible transformation that can be employed to facilitate the preparation of metallated enol ethers (Scheme 102).[154] This was achieved initially by a β-elimination reaction of a carbohydrate derivative **382** to give the sulfoxide **383**.



Scheme 102: Sulfoxide-lithium exchange

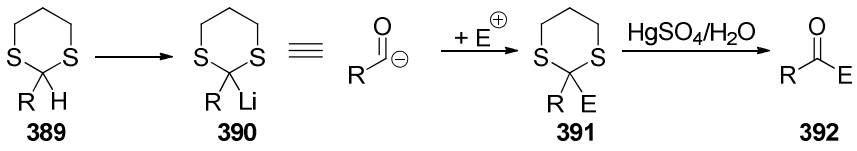
This has the advantage of being more environmentally friendly than the tin chemistry, and is efficient however the requirement of a β-elimination for the vinyl sulfoxide preparation reduces the substrate scope.

To overcome the requirement for β-elimination Kocienski *et al.* have shown that starting from the lactone **385**, preparing the enol triflate **386** or phosphate and then coupling this with sodium arene thiolate in the presence of nickel will give the thioether **387**.[155] Subsequent slow addition of *m*-CPBA afforded the sulfoxide **388** (Scheme 103). The sulfoxide was stable to column chromatography and can be stored for several months, unlike the sulfide.



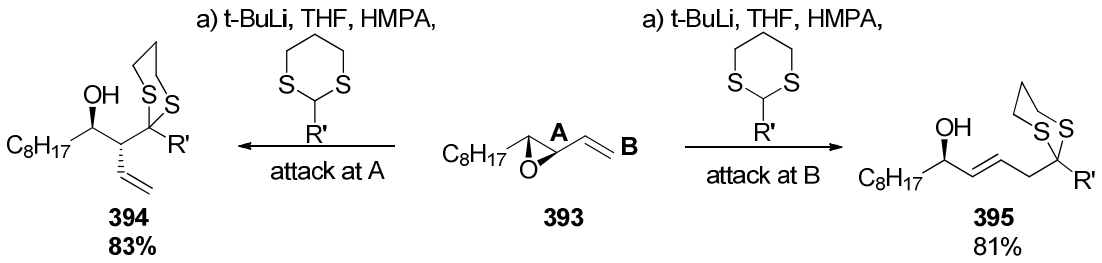
Scheme 103: Ni-catalysed coupling of enol triflate 386 derived from lactone 385

2-Lithio-1,3-dithiane derivatives **390** are some of the most widely-used sulfur-stabilised acyl anion equivalents as demonstrated by Corey and Seebach (Scheme 104).[156]



Scheme 104: Nucleophilic attack of a dithiane

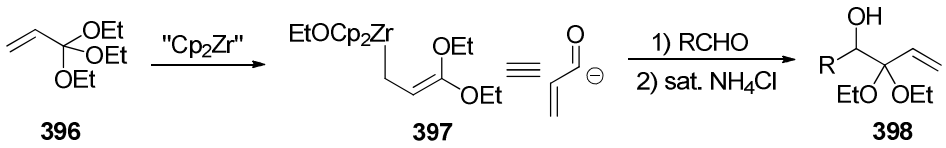
Recently Amos Smith *et al.* have achieved high chemoselectivity with vinyl epoxides by taking advantage of the steric properties of the dithiane. It has been shown that the vinyl epoxide **393** will undergo attack at the allylic position **A** to give **394** if R' is small (R = H) whereas if R' is large (R = ^{i}Pr) attack will occur at the terminal end of the alkene **B** to give **395** as outlined in Scheme 105.[157]



Scheme 105: Preferential attack of nucleophiles with differing steric properties

5.2.2. Other α,β-unsaturated acyl anion equivalents

It has been shown by Ito and Taguchi that allylic zirconium species can be used as α,β-unsaturated acyl anion equivalents (Scheme 106).[158] Preparation of γ,γ-dialkoxyallylic zirconium species **397** can be achieved by the reaction of triethyl orthoacrylate with a zirconocene equivalent. The reaction proceeds *via* the formation of a zirconacyclopropane intermediate followed by the β-elimination of an alkoxy group.

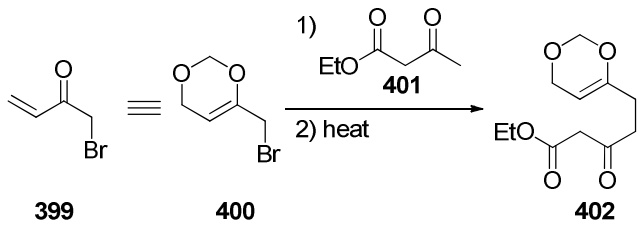


Scheme 106: Preparation of γ,γ-dialkoxyallylic zirconium species

This reaction worked well with a range of aromatic aldehydes but with α,β-unsaturated aldehydes lower yields were obtained.

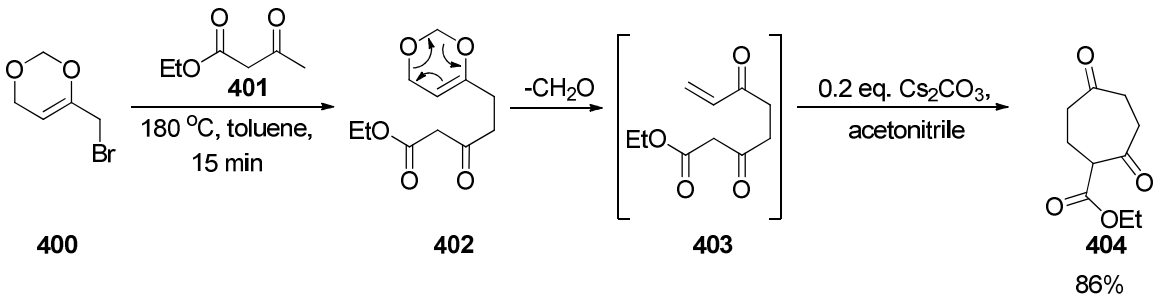
5.3 Uses of 4*H*-1,3-Dioxins in synthesis

Substituted 4*H*-1,3-dioxins have recently been shown to be effective equivalents of α,β-unsaturated carbonyl compounds as outlined by Funk.[132] 6-Bromomethyl-4*H*-1,3-dioxin **400** was used as a masked equivalent of an unstable bromomethyl vinyl ketone **399** (Scheme 107).



Scheme 107: Masked vinyl ketone reacting with nucleophile

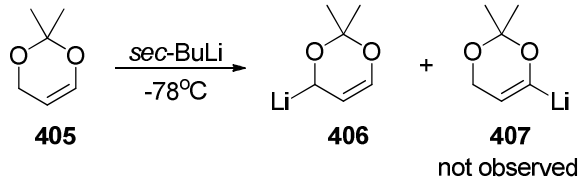
The bromide **400** underwent the usual substitution reaction, permitting facile introduction of a basic nucleophile **401** (Scheme 108). The remaining β-nucleophilic site could then be exposed simply by heating to facilitate the retrocycloaddition reaction, allowing for nucleophilic attack at the β-position to give the cyclic ketone **404**.



Scheme 108: Retro-cycloaddition to reveal desired ketone

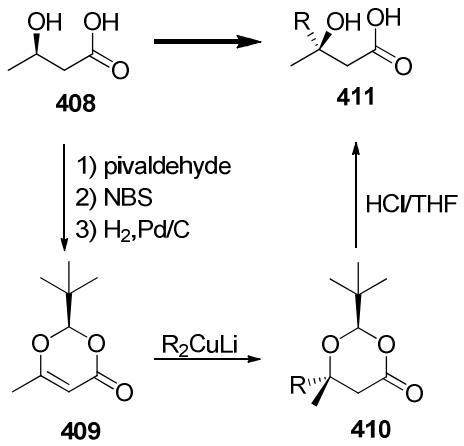
The acyl anion equivalent outlined in (Figure 12, page 79) cannot be easily synthesised from lithiation of the parent unsaturated system below. Funk has shown that when dioxin

405 is reacted with *sec*-butyllithium, the metallated dioxin **406** is the sole product with no formation of **407** (Scheme 109).[159]



Scheme 109: Lithiation of acyl dioxin

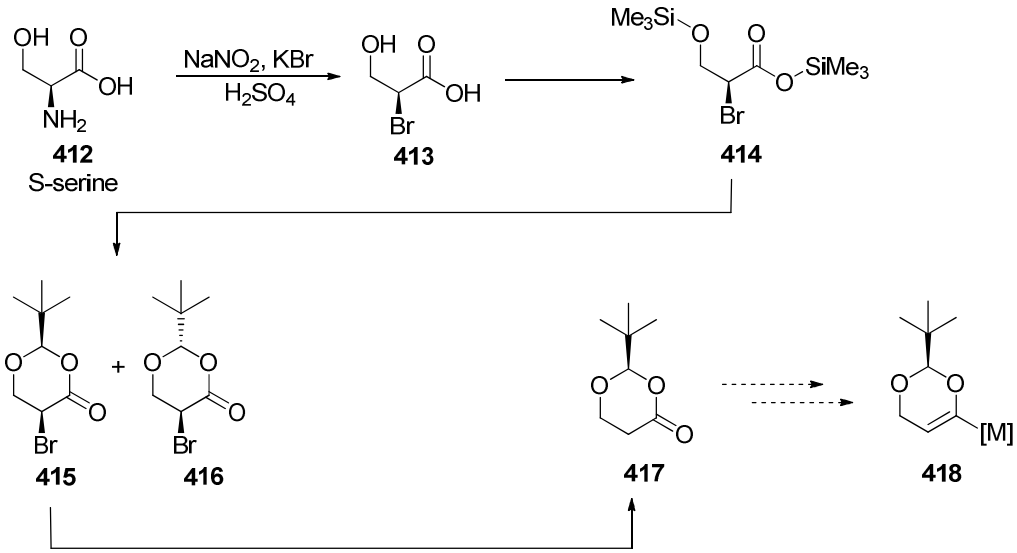
Seebach has developed the use of 1,3-dioxanones in asymmetric synthesis from the alkylation of 3-hydroxy-carboxylic acids (Scheme 110).[160] Previously, alkylation of carboxylic acids was achieved by utilising dilithio-alkoxide enolates. The dioxanone method is superior as only 1 equivalent of strong base is required, the products are crystalline and facile preparation of both *R* and *S* configurations is possible.



Scheme 110: Seebach's self-reproduction of stereogenic centres

The acid-catalysed reaction of (*R*)-3-hydroxy-butyric acid **408** with pivaldehyde gives **409**. The lithium enolate that is generated from **409** is stable at -75 ˚C and does not undergo β-elimination. The Michael addition of dialkyl cuprates gives only one product **410**. The enantiopure hydroxy-acid product **411** is revealed by unmasking **410** using a mild acid.

Seebach has extended this work further by using readily available amino acids as starting materials to allow the preparation of brominated dioxanones (Scheme 111)[161] Retentive nucleophilic substitution of serine followed by silylation leads to an intermediate **414**. This undergoes TMS-triflate catalysed acetalisation of pivaldehyde to give a mixture of two diastereoisomers which are separable by column chromatography. Catalytic hydrogenative debromination of the *cis*-isomer affords the enantiomerically pure derivative of 3-hydroxypropanoic acid **417**.



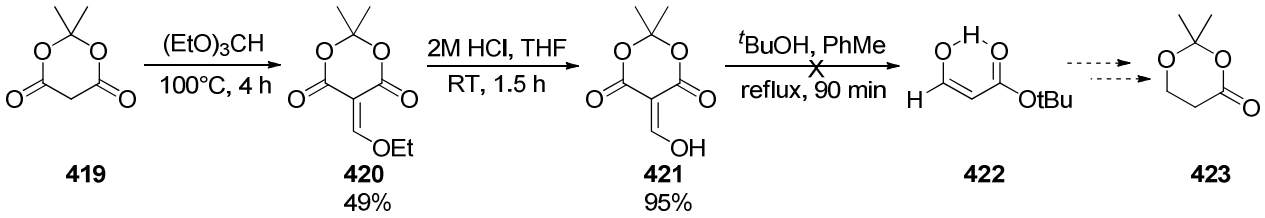
Scheme 111: Chiral β-Hydroxypropanoic-Acid Derivative from Serine

We hope that the dioxinone **417** could be converted to an acyl anion intermediate by reduction of the lactone followed by elimination to give the unsaturated intermediate **418**.

5.4 Applications of Meldrum's Acid to facilitate lactone formation

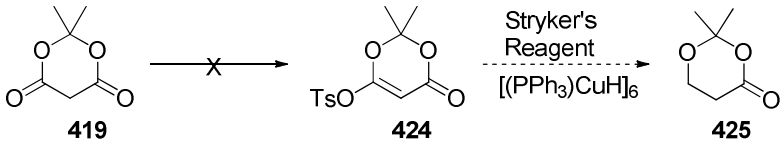
It was envisaged that **423** (Scheme 112) could be synthesised from the commercially available Meldrum's Acid **419**. The formation of formylated Meldrum's Acid **421** was achieved by reacting Meldrum's Acid **419** with triethylorthoformate to give the intermediate **420** which was then reacted with hydrochloric acid to give the formylated

Meldrum's Acid **421**.[162, 163] This was reacted with ^{t}BuOH but did not yield the formylacetic ester **422**.[164]



Scheme 113: Attempted synthesis of a formylacetic ester 422

The preparation of a tosylated Meldrum's Acid **424** was attempted using conditions outlined by Tanabe *et al*. for effective preparation of β-ketoester enol tosylates (Scheme 114).[165] They report the formation of a highly reactive *N*-sulfonylammonium intermediate from tosylchloride and NMI. Several variations of the reaction conditions were tested but to no avail. This would have been beneficial as once the intermediate **424** was formed it would have been potentially possible to do a conjugate reduction-elimination with Stryker's reagent. A further reduction would afford the lactone **425** which could be converted to the acyl anion equivalent as outlined in Scheme 90, (page 81).

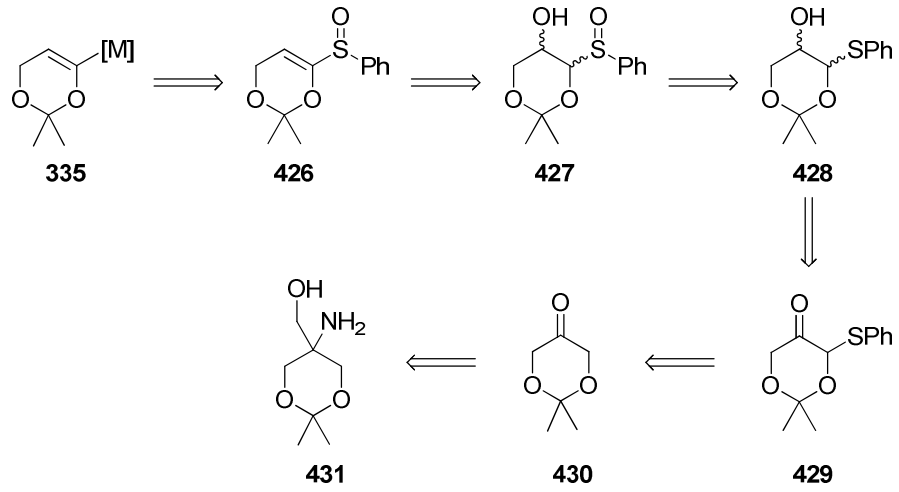


Scheme 114: Attempts to prepare lactone 425 using Stryker's reagent

The tosylation of Meldrum's acid **419** was attempted using various bases (triethylamine, 2,6-lutidine and potassium *tert*-butoxide). Tosyl chloride (1.1 to 1.5 equivalents) was used as the tosylating agent. NMI was added in an effort to promote the tosylation and halogenated solvents (dichloromethane and chlorobenzene) were used. The reaction was attempted at 0 $^{\circ}$C and room temperature for varying times and no combination of reaction conditions yielded **424**.

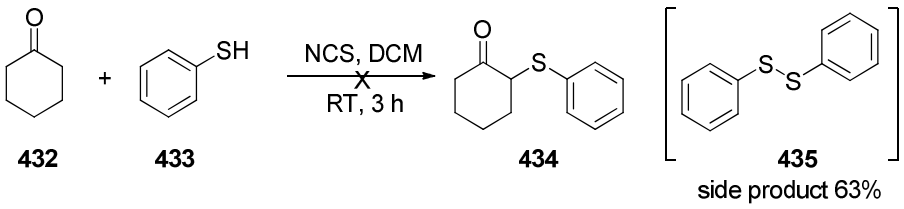
5.5 Cyclic ketones as a potential route to metallated dioxins

The route below (Scheme 115) was then considered as a possible pathway to metallated dioxin **335**. Starting from the amine **431** oxidative cleavage would afford ketone **430**. Sulfenylation of **430** would give **429** which would subsequently be reduced to yield intermediate **428**. This could be converted to the sulfonated moiety **427**. An elimination reaction would give **426** and with a metal-sulfoxide exchange would give the metallated dioxin **335**.



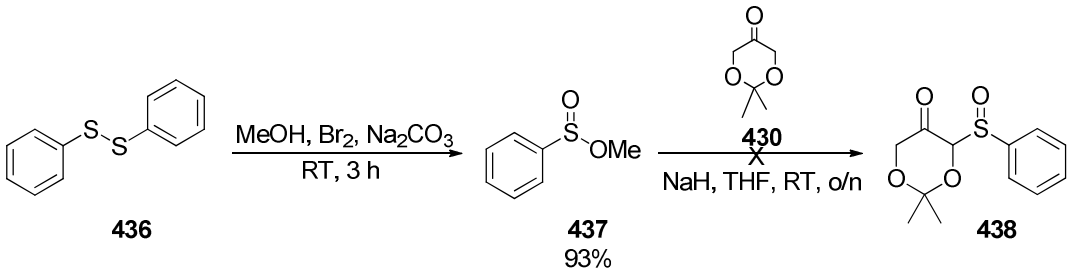
Scheme 115: Retrosynthetic analysis of metallated dioxin 335

Yadav *et al.* report α-sulfenylation of cyclohexanone **432** in the presence of thiophenol **433**.[166] However, in our hands, the reaction led only to the formation of a side product, diphenyl disulfide **435**, therefore the reaction was not attempted with the cyclic ketone **430** (Scheme 115).



Scheme 116: Sulfenylation of cyclohexanone 432

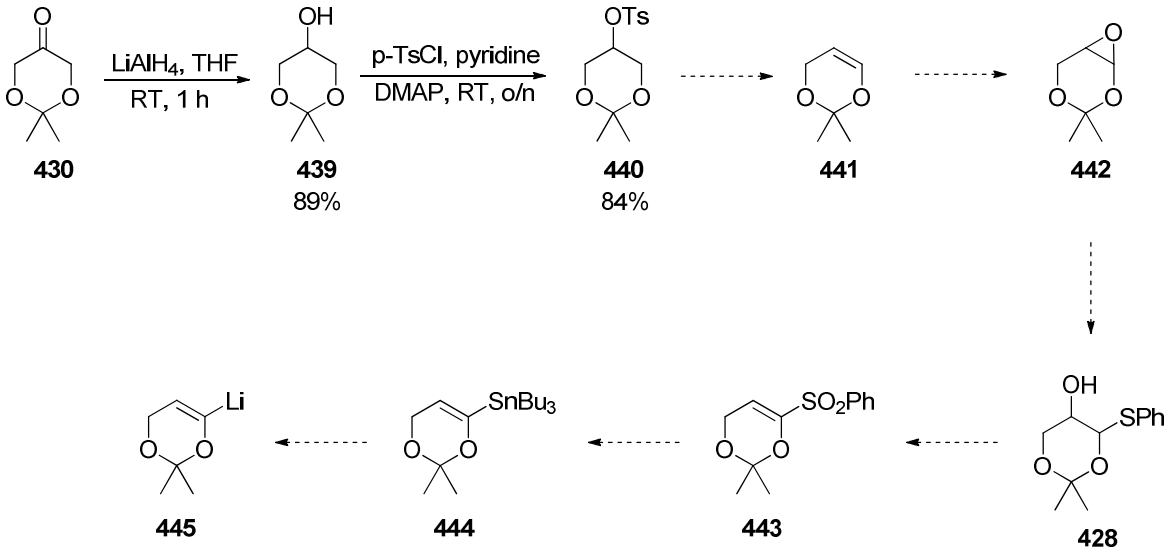
Monteiro and Souza prepared β-keto-phenylsulfoxides from the corresponding ketone (Scheme 117).[167] The reaction was attempted using the cyclic ketone **430** and methyl benzenesulfinate **438**. The starting material was consumed and there was no sign of product **439** by NMR analysis.



436 **437** 93% **438**

Scheme 117: Attempted α-sulfinylation of cyclic ketone 430

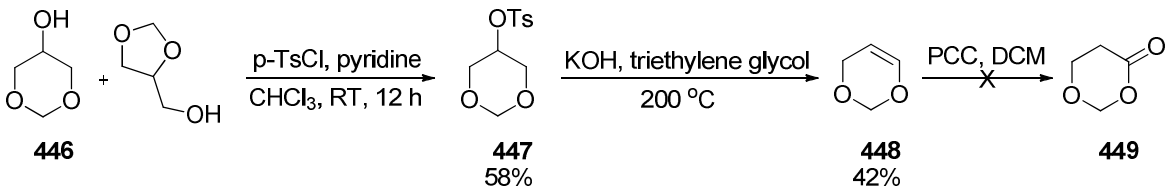
It was of interest to investigate the transformation of the cyclic ketone to the tosylate **440** as this was considered a potential route to the dioxene **441** which could be converted to the metallated dioxin **445** as shown in Scheme 118. This reaction was carried out by treatment of **430** with $LiAlH_4$ to give the alcohol **439** which was subsequently reacted with *p*-toluenesulfonyl chloride and pyridine in the presence of a catalytic amount of DMAP to give **440**. If **441** had been formed reaction with dimethyldioxirane would have afforded the epoxide **442**. Ring opening of **442** with thiophenol would give **428**. The stannane **444** could have been prepared from the sulfone **443** by Ni-catalysis.



Scheme 118: Preparation of the tosylate 85 from the corresponding cyclic ketone 430

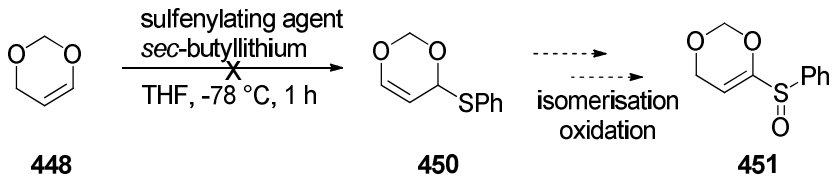
5.5.1 Dioxene Chemistry

It was envisaged that another potential route to lactone **449** could be achieved *via* a dioxin intermediate **448** (Scheme 119).[168] Glycerol formal **446** was reacted with *p*-toluenesulfonyl chloride and purification by crystallisation gave solely the 6-membered ring product **447**. This then underwent an elimination reaction to give the dioxin **448**. Pyridinium chlorochromate proved ineffective for the oxidation of the dioxin **448** to yield **449**.[169] This reaction was difficult to monitor as dioxene **448** has a low b.p. of 76 °C. The reaction was monitored by GC and there was no sign of a less volatile product being formed.



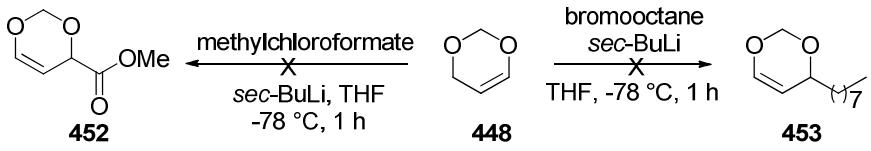
Scheme 119: Potential route to lactone 449

The route below (Scheme 120) was attempted as Funk and Bolton have shown that 4*H*-1,3-dioxins can undergo exclusive allylic deprotonation with *sec*-butyllithium.[170] A range of sulfenylating agents were screened, diphenyl disulfide **436**, phenylsulfenyl chloride and phenyl benzenethiosulfonate but all were unsuccessful.



Scheme 120: Attempted preparation of sulfenylated 4*H*-1,3-dioxins

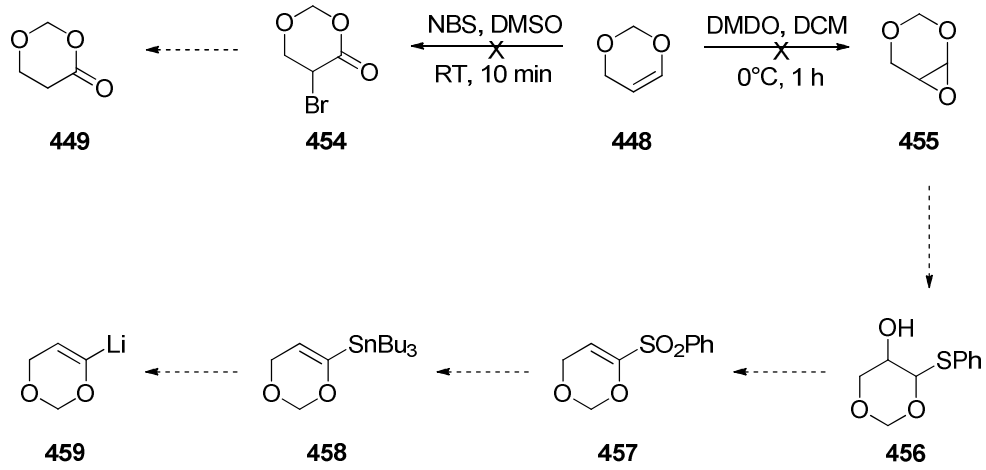
Alkylation of the dioxin **448** (Scheme 121) was unsuccessful in the presence of methyl chloroformate. However, alkylation using bromooctane was successful giving rise to a less volatile material. This material was impossible to purify by column chromatography as the bromooctane and product co-elute on silica. Vacuum distillation did not lead to the complete removal of bromooctane.



Scheme 121: Attempts to alkylate dioxin 448

It was envisaged that epoxidation of dioxin **448** followed by ring opening in the presence of a sulfenylating reagent would give rise to the sulfenylated intermediate **456** (Scheme 122). Epoxidation of dioxin **448** was attempted using dimethyldioxirane but this proved unsuccessful.[171] This was again difficult to monitor as the starting material was volatile. Dioxene **448** could potentially undergo oxidative halogenation to give **454**, followed by a bromide reduction to give lactone **449**. The oxidative halogenation of dioxin **448** looked promising by NMR of the crude reaction material (signal between 3-3.5 ppm).[172]

However, upon attempted purification by column chromatography no desired material was recovered.

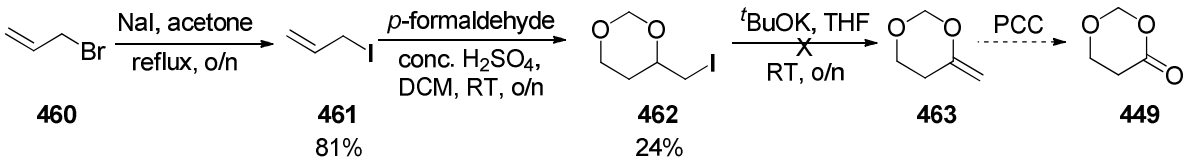


Scheme 122: Potential transformations of the dioxene 448

Due to volatility of the dioxin **448**, a limiting amount of *N*-bromosuccinimide was used so TLC analysis monitoring the consumption of NBS could be achieved. Dihydropyran, 2,3-dihydrofuran and dioxin **448** were all tested for their reactivity in the presence of NBS (0.9 equiv.). The reaction was carried out in DMSO (0.5 M) at room temperature for 2-22 hours. The starting material was consumed in the case of the dioxin **448**. No diagnostic signal at 3-3.5ppm corresponding to an α-proton next to the bromine for 2,3-dihydrofuran was seen in the NMR. Dihydropyran gave an unidentifiable mixture. Due to these unpromising results it was decided to no longer attempt this transformation.

5.6 Unsaturated Cyclic Acetal Formation

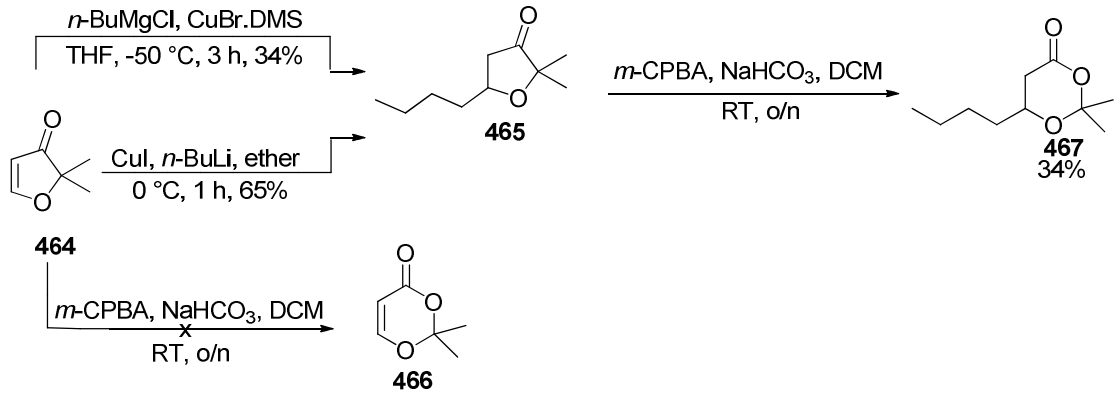
A potential route to lactone **449** was undertaken starting from allyl bromide **460** (Scheme 123). Allyl bromide **460** was converted to allyl iodide **461** in a 77% yield.[173] This was then converted to the cyclic acetal **462** in the presence of paraformaldehyde as outlined by Greshock and Funk.[132] Initial attempts to form the exocyclic alkene **463** were unsuccessful and gave an inseparable mixture of starting material **462** and cyclic alkene **463**. In the presence of PCC this did not afford lactone **449**.



Scheme 123: Possible new route to lactone 449

5.6.1 Lactone formation from furanones

Another potential route that we investigated is outlined in Scheme 124, to form lactone **467.** This would provide a less volatile lactone compared to **449**. It was necessary to alkylate the furanone **464** initially in order to avoid volatile intermediates that could have proved problematic to isolate. Conjugate addition to the cyclic furanone **464** was first attempted using *n*-butyl magnesium chloride and CuBr.DMS.[174] On a small scale (74 mg) this gave a 34% yield. This was not reproducible on a larger scale. Smith *et al.* have shown that furanone **464** will undergo organocuprate addition to give **465**, and this was achieved giving the desired product in a 65% yield.[175] The cyclic ketone **465** underwent a Baeyer-Villiger oxidation to give the lactone **467** in a 34% yield. Direct Baeyer-Villiger oxidation from the furanone **464** was attempted using the same conditions as employed for the oxidation of the saturated structure but this did not afford **466**. Instead an unidentifiable mixture was obtained.



Scheme 124: Conjugate additions and Baeyer-Villiger oxidations of the cyclic enone 464 and its derivatives.

As a control the lactone **467** was stirred in the presence of PCC for 2 hours and there were no signs of decomposition by NMR after this time. The stability of the acetal group in **467** to PCC and similar reagents was unknown. This suggests lactone **449** (Scheme 119) would most likely be stable if formed.

5.6.2 Attempted preparation of an acyl anion equivalent from commercially available 2,2,6-trimethyl-1,3-dioxin-4-one 468

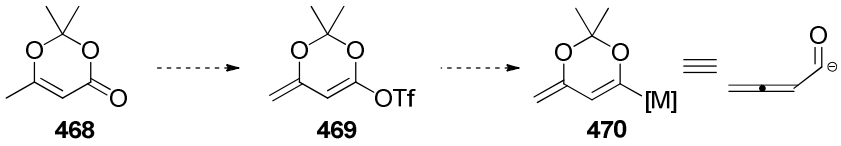
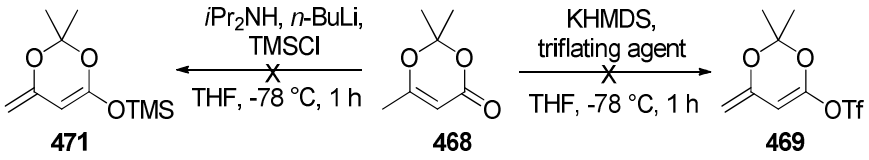


Figure 14: Possible acyl anion equivalent from 468

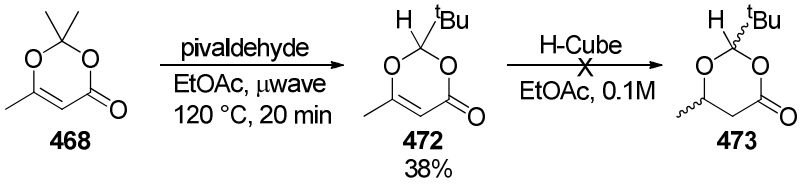
Kocienski *et al.* have shown conversion of enol triflates to lithium enolates by the addition of Lipshutz mixed cuprate (Scheme 101, page 87). We hoped to form enol triflate **469** from the commercially available **468**. If the triflate **469** was converted to the metallated compound **470** (Figure 14) this would give a novel acyl anion equivalent.

Clive and Minaruzzaman[176] converted a lactone to an enol triflate using KHMDS and 2-[N,N-bis(trifluoromethylsulfonylamino]pyridine. It was thought this methodology would be used to yield **469** (Scheme 125). The triflate **469** could be transformed to the corresponding stannane and this would undergo a sulfoxide-lithium exchange to give a metallated dioxin similar to that outlined in Figure 14. Unfortunately, these reaction conditions did not lead to trapping of **469**. Attempted silylation in the presence of LDA also gave no sign of **471**.[177]



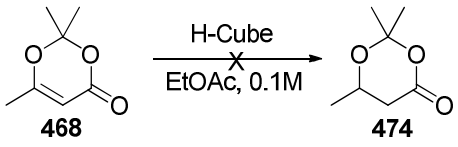
Scheme 125: Attempted triflation of the commercially available dioxinone 469

Seebach and Zimmermann hydrogenated the substrate **472** with H_2 (30 atm, PtO_2). The substrate **472** was synthesised and a PtO_2 catalyst was used in the H-Cube.[160] It seemed that the H-Cube being a flow reactor may not have been suitable for the hydrogenation due to low exposure times of the reactant with the catalyst. Slower flow rates still produced only unreacted starting material **472**.



Scheme 126: Preparation of 472 and the subsequent attempted hydrogenation

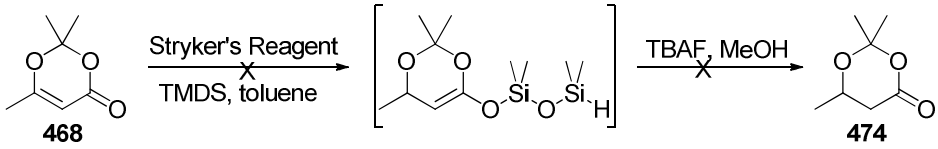
Hydrogenation of the commercially available dioxinone **468** was attempted (Scheme 127). Several different catalysts (Raney-Ni, Palladium on charcoal and palladium hydroxide on charcoal) were tested for the hydrogenation of dioxinone **468** using the H-Cube hydrogenation flow reactor and the reaction conditions were also altered (50 bar-80 bar and room temperature to 80 °C). In each case starting material was recovered with no conversion observed at all. It was considered that the two methyl groups in dioxinone **468** may have caused steric difficulties in the interaction with the catalyst.



Scheme 127: Hydrogenation attempts of dioxinone 468

Another possible way to reduce the dioxinone **468** would be to employ Stryker's reagent (Scheme 128).[178] Stryker's reagent ($[(PPh_3)CuH]_6$) is a mild source of hydride and is used in the reduction of enones, enol esters and related substrates. Lipshutz *et al.* have shown that exposure of an enone to a catalytic quantity of Stryker's reagent in the presence of a silane leads to conjugate reduction with concomitant formation of the

corresponding silyl enol ether. Without isolation treatment of these intermediates with an activated fluoride source would give the reduced product. When dioxinone **468** was treated with Stryker's reagent overnight TLC showed starting material still present. TBAF was added to one test reaction and no reduction was observed. It may be that the reduction conditions were too mild to facilitate the desired transformation.

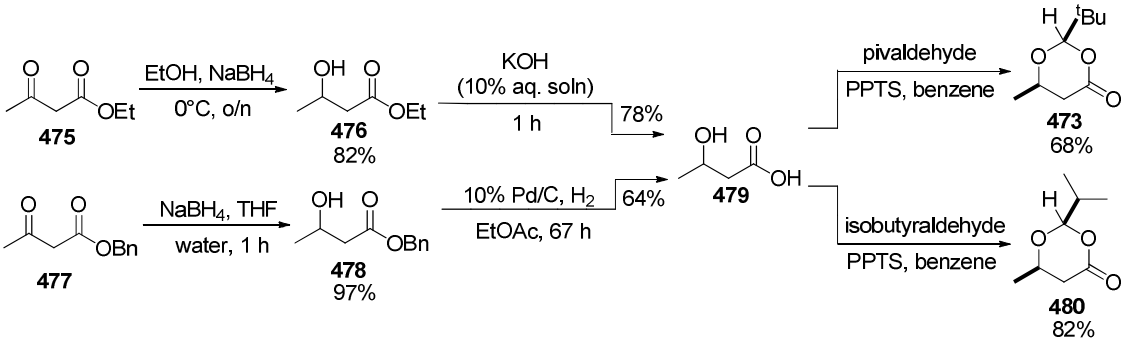


Scheme 128: Attempted reduction with Stryker's Reagent

5.6.3 Preparation of Dioxinones to test Dioxin Formation Methodology

Seebach *et al.* have shown that dioxinones can be formed from 3-hydroxybutanoic acid **479** (Scheme 129) and the corresponding aldehyde in the presence of pyridinium *p*-toluenesulfonate. The cyclic acetals **475** and **480** are of interest as they are structurally similar to the cyclic lactone **344** and would provide a means by which to test the methodology outlined in Scheme 90.

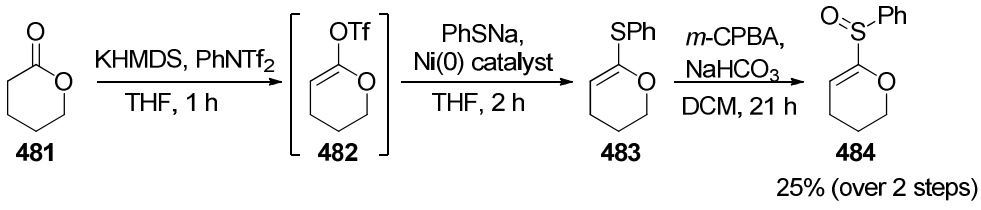
Initially 3-hydroxybutanoic acid **479** was formed starting from ethyl acetoacetate **475** undergoing a reduction to give **476** as shown by Padhi and Chadha[179] followed by an ester hydrolysis. The acid **479** was difficult to isolate from the aqueous work up due to the polarity of the material and column chromatography was not favourable on a large scale. Therefore **479** was synthesised from benzylacetoacetate **477** instead. The benzyl ester was easier to isolate and required no further purification. The hydrogenation of **478** to **479** gave a purer sample of **479**.



Scheme 129: Preparation of the cyclic acetals 473 and 480

Initially **480** was synthesised from the acid **479** but purification was problematic as the product decomposes on silica and a dry-ice bath recrystallisation was necessary to isolate the product which is a liquid at room temperature. It was decided that **473** would be synthesised as it was envisaged that recrystallisation would be more facile (m.p. 82°C). Recrystallisation of **473** proved much easier than **480** so work focussed on this substrate.

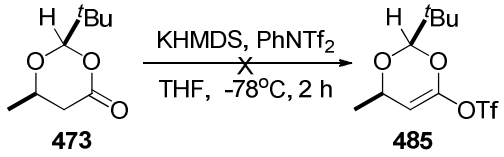
With dioxinone **473** in hand we were able to attempt conversion to the acyl anion equivalent. As a control reaction, the commercially available δ-valerolactone **481** was triflated to give **482** using the procedure of Kocienski (Scheme 130). The intermediate could be identified by NMR (dd, 4.7 ppm) however purification of this material by column chromatography led to decomposition.



Scheme 130: Sulfoxidation of δ-valerolactone 481

The crude triflate **482** was therefore reacted on without purification to give the sulfenylated enol ether **483**. This was oxidised in the presence of *m*-CPBA. This transformation of δ-valerolactone **481** to the corresponding sulfoxide **484** was of interest as it confirms that cyclic lactones are able to undergo triflation and subsequent

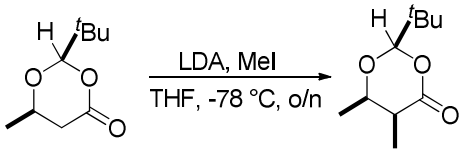
transformations and it was therefore anticipated that the cyclic acetal **473** would perhaps have similar reactivity to that shown for δ-valerolactone **481**.



473 **485**

Scheme 131: Attempted triflation of cyclic acetal 473

Triflation of **473** was first attempted using KHMDS to form the potassium enolate intermediate and employing *N*-phenyl-bis(trifluoromethanesulfonimide) as the triflating agent (Scheme 131). This was unsuccessful so LiHMDS/HMPA was used instead of KHMDS in the hope that the lithium enolate would be more stable and the desired product would be formed. However this was not the case. It was of interest to investigate this reaction further as it was unclear whether the enolate was being formed at all or if the starting material was just decomposing under these reaction conditions. Alkylation of **473** was achieved as outlined by Seebach and Zimmermann[160] in Scheme 132. It seems that the lithium enolate of **473** formed from reaction with LDA is stable. It may be that a more reactive triflating reagent is required to produce the desired enol triflate.

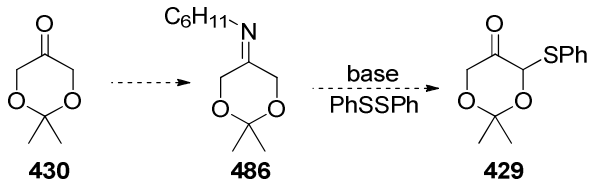


473 **485**
62%

Scheme 132: Alkylation of 430

5.7 Conclusion and possible avenues for future investigation

Sulfenylation of the cyclic ketone **430** (Scheme 133) was problematic as was the sulfenylation of the dioxene **448**. Aungst, Jr. and Funk have shown α-alkylation of the cyclic ketone **430**, by first converting the ketone to an imine.[180] This suggests that sulfenylation is probably not as straight forward as first anticipated. Sulfenylation could be attempted following the alkylation methodology outlined by Funk *et al.*



Scheme 133: Sulfenylation of cyclic lactone 430

Although δ-valerolactone **481** can be converted to the corresponding sulfoxide **484** (Scheme 130), the initial triflation of the cyclic acetal **473** was difficult. Having two additional carbon-oxygen bonds in the acetal ring may lead to too much strain being incurred to allow for introduction of a triflate group in the formation of **485**.

Investigations could have been carried out to ascertain the stability of the lithium and potassium enolates of **473** and the ease of alkylation and triflation of these moieties. Successful triflation would have permitted the methodology outlined in Scheme 90 (page 81) to be tested.

However, as the viability of this method had not been demonstrated after approximately one year of investigation, the project was changed and the sulfamidate work was undertaken.

Chapter 6

Experimental

Chapter Six - Experimental

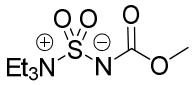
6.1 General procedures

^{1}H NMR spectra were recorded on Bruker AV 300, DPX 400 and AV 400 spectrometers at 300 and 400 MHz respectively and referenced to residual solvent. ^{13}C NMR spectrum were recorded using the same spectrometers at 75 and 100 MHz respectively. Chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS) or to residual solvent peaks ($CDCl_3$ at δ_H 7.26). *J* values are given in Hz and s, d, dd, t, q and m abbreviations correspond to singlet, doublet, doublet of doublet, triplet, quartet and multiplet. Mass spectra were obtained at the EPSRC National Mass Spectrometry Service Centre in Swansea. Infrared spectra were obtained on Perkin-Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory, deposited neat or as a chloroform solution to a diamond/ZnSe plate.

Flash column chromatography was carried out using Matrix silica gel 60 from Fisher Chemicals and TLC was performed using Merck silica gel 60 F254 precoated sheets and visualised by UV (254 nm) or stained by the use of aqueous acidic $KMnO_4$. Anhydrous dichloromethane (DCM) and anhydrous dichloroethane (DCE) was distilled from CaH_2.

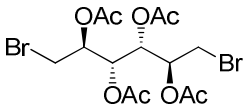
6.1.1 Experimental for Chapter 2

Burgess reagent (119)[92]



Anhydrous methanol (2.5 g, 3.1 mL) in benzene (30 mL) was added dropwise to a solution of chlorosulfonyl isocyanate (10 g, 71 mmol) in benzene (30 mL) dropwise over 30 minutes. The reaction mixture was concentrated in vacuo and the carbomethoxysulfamoyl chloride was dissolved in benzene (170 mL) and was added dropwise to a solution of triethylamine (18.0 g, 178 mmol) in benzene (80 mL). After the addition was complete (1 hour), the mixture was filtered. The filtrate was concentrated in vacuo to afford the title compound as a white solid (15.8 g, 67 mmol, 94%). δ_H (300 MHz, $CDCl_3$) 3.70 (s, 3H), 3.47 (q, *J* = 7.3 Hz, 6H), 1.41 (t, *J* = 7.3 Hz, 9H); δ_C (75 MHz, $CDCl_3$) 157.8 (C=O), 55.7 (CH_2), 51.2 (CH_3), 9.6 (CH_3); m.p. 76 °C (lit. m.p. 76-79 °C).

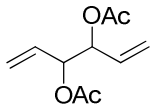
(2S,3S,4S,5S)-1,6-dibromohexane-2,3,4,5-tetrayl tetraacetate (198)[181]



D-mannitol **197** (20 g, 0.1 mol) was suspended in dry dioxane (150 mL). Acetyl bromide (32.4 g, 19.5 mL, 0.3 mmol) was added slowly and stirred for 4 days at room temperature. The solution was heated to 40 °C and stirred for 4 hours. The room temperature reaction mixture was concentrated *in vacuo*. The residue was dissolved in dry pyridine (100 mL) and acetic anhydride (89.6 g, 82 mL, 0.9 mol) was added slowly. The reaction mixture was stirred overnight, concentrated *in vacuo* and recrystallised using ethanol affording the title compound as a white solid (18.9 g, 39.6 mmol, 36%). δ_H (300 MHz, $CDCl_3$) 5.42 (d, *J* = 8.3 Hz, 2H), 5.18 – 5.04 (m, 2H), 3.55 (dd, *J* = 11.6, 3.6 Hz, 2H), 3.36 (dd, *J* = 11.6,

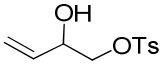
6.0 Hz, 2H), 2.12 (d, J = 3.2 Hz, 12H); δ_C (75 MHz, $CDCl_3$) 169.8 (C=O), 169.7 (C=O), 69.1 (CH), 68.9 (CH), 30.6 (CH_2), 20.8 (CH_3), 20.7 (CH_3); ν_{max}/cm^{-1} 2976, 1746, 1428, 1370, 1207, 1045; m.p. 77 °C (lit. m.p. 76-78 °C).

Hexa-1,5-diene-3,4-diyl diacetate (199)[93]



(2*S*,3*S*,4*S*,5*S*)-1,6-Dibromohexane-2,3,4,5-tetrayl tetraacetate **198** (7.0 g, 14.7 mmol) was dissolved in glacial acetic acid (70 mL). Sodium acetate (4.4 g, 32.3 mmol) and zinc dust (3.9 g, 58.8 mmol) were added. The mixture was heated to 110 °C until the evolution of gas ceased and the solution became clear (1 hour). After cooling, the zinc dust was filtered off and the acetic acid removed under reduced pressure. The residue was dissolved in water and extracted with diethyl ether (3 x 50 mL). The combined organic layer was washed with saturated sodium bicarbonate solution, dried ($MgSO_4$) and concentrated *in vacuo* affording the title compound as a yellow oil (2.9 g, 14.7 mmol, 99%). δ_H (300 MHz, $CDCl_3$) 5.76 (ddd, J = 15.0, 10.5, 5.4 Hz, 2H), 5.44 – 5.22 (m, 6H), 2.08 (s, 6H); δ_C (75 MHz, $CDCl_3$) 169.8 (C=O), 132.1 (CH), 119.2 (CH_2), 74.4 (CH), 20.9 (CH_3); b.p. 70 °C at 5 mbar (lit. b.p. 59-61°C at 0.8 mbar).

2-Hydroxybut-3-en-1-yl 4-methylbenzenesulfonate (205)[182]

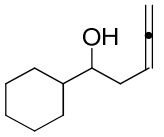


3,4-Dihydroxy-1-butene **204** (1.5 g, 17.0 mmol) was dissolved in pyridine (90 mL). At -20 °C, tosyl chloride (3.9 g, 20.4 mmol) in pyridine (45 mL) was added dropwise over 40 minutes. The mixture was allowed to reach room temperature over 2 hours and stirred for 20 hours. The mixture was concentrated *in vacuo* and dissolved in ethyl acetate. The

solution was washed with water, hydrochloric acid (1M), saturated sodium bicarbonate solution and brine. The reaction mixture was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (2:1 petroleum ether/ethyl acetate) afforded the title compound as a colourless liquid (2.9 g, 11.8 mmol, 69%). δ_H (300 MHz, $CDCl_3$) 7.82 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 5.78 (ddd, *J* = 17.2, 10.6, 5.5 Hz, 1H), 5.40 (dt, *J* = 17.3, 1.2 Hz, 1H), 5.27 (dd, *J* = 10.5, 1.2 Hz, 1H), 4.44 – 4.35 (m, 1H), 4.09 (dd, *J* = 10.2, 3.4 Hz, 1H), 3.93 (dd, *J* = 10.3, 7.4 Hz, 1H), 2.47 (s, 3H); δ_C (400 MHz, $CDCl_3$) 145.4 (C), 134.9 (C), 132.4 (CH), 128.9 (CH), 127.5 (CH), 117.9 (CH_2), 72.7 (CH), 70.0 (CH_2), 21.6 (CH_3); ν_{max}/cm^{-1} 2359, 1206, 1147, 758, 749.

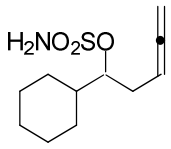
6.1.2 Experimental for Chapter 3

1-Cyclohexylpenta-3,4-dien-1-ol (215)[183]



1-Cyclohexylbut-3-yn-1-ol **214** (1.2 g, 7.6 mmol), paraformaldehyde (522 mg) diisopropylamine (2.21 mL, 1.58 g, 15.66 mmol) and dry dioxane (20 mL) were placed in a round bottomed flask. Copper(I) bromide (362 mg, 4.35 mmol) was added to the stirring solution and the solution refluxed for 5 hours. The reaction mixture was filtered through silica with diethyl ether. Purification by column chromatography (8:1 petroleum ether / ethyl acetate to ethyl acetate) giving the desired material as a yellow oil (210 mg, 1.3 mmol, 15%). δ_H (400 MHz, $CDCl_3$) 5.18-5.12 (m, 1H), 4.75 – 4.67 (m, 2H), 3.49 – 3.37 (m, 1H), 2.33 – 2.20 (m, 1H), 2.18 – 2.04 (m, 1H), 1.95 – 1.81 (m, 1H), 1.81 – 1.70 (m, 1H), 1.70 – 1.60 (m, 2H), 1.46 – 1.32 (m, 2H), 1.32 – 0.97 (m, 6H); δ_C (75 MHz, $CDCl_3$) 209.3 (C), 86.7 (CH), 75.3 (CH), 74.8 (CH_2), 43.0 (CH), 33.6 (CH_2), 29.1 (CH_2), 28.1 (CH_2), 26.5 (CH_2), 26.3 (CH_2), 26.2 (CH_2); ν_{max}/cm^{-1} 3380, 3052, 2923, 1949, 836.

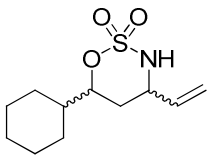
1-Cyclohexylpenta-3,4-dien-1-yl sulfamate (216)



Under an inert atmosphere (nitrogen), formic acid (87 µmol, 2.3 mmol) was added drop wise to chlorosulfonyl isocyanate (0.2 mL, 2.3 mmol) with vigorous stirring at 0 °C. Acetonitrile (1.2 mL) was added and the reaction mixture warmed to room temperature

and stirred overnight. The reaction mixture was cooled to 0 °C and a solution of 1-cyclohexylpenta-3,4-dien-1-ol **215** (220 mg, 1.3 mmol) in dimethylacetamide (0.5 mL). The reaction mixture was stirred for 24 hours. The reaction mixture was diluted using diethyl ether (2 mL) and quenched with saturated sodium chloride solution (1 mL). This was added to a solution of diethyl ether (4 mL) and water (1.5 mL). The separated aqueous phase was further extracted with diethyl ether (2 mL). The combined organic phase was washed with saturated sodium chloride solution (2 x 1.5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (8:1 petroleum ether/ethyl acetate to 4:1 petroleum ether/ethyl acetate) afforded the title compound as a white solid (191 mg, 0.8 mmol, 60%). δ_H (400 MHz, $CDCl_3$) 5.20 – 5.13 (m, 1H), 4.79 – 4.73 (m, 2H), 4.68 (s, 2H), 4.52 – 4.47 (m, 1H), 2.63 – 2.41 (m, 2H), 1.95 – 1.66 (m, 6H), 1.37 – 1.03 (m, 5H); δ_C (75 MHz, $CDCl_3$) 209.6 (C), 88.2 (CH), 85.0 (CH), 75.1 (CH_2), 40.4 (CH), 30.6 (CH_2), 28.6 (CH_2), 27.9 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 25.9 (CH_2); ν_{max}/cm^{-1} 3277, 2927, 2854, 1645, 1408, 1361, 1175, 870; m/z (ESI^+) 280 (M + Cl^-, 100%), 244 (70%); HRMS (ESI^+) found 280.0774, $C_{11}H_{19}O_3NClS$ (M + Cl)$^-$ requires 280.0780.

6-Cyclohexyl-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide (217)

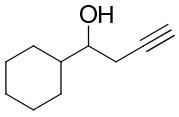


Under an inert atmosphere (nitrogen), 1-cyclohexylpenta-3,4-dien-1-yl sulfamate **216** (50 mg, 0.20 mmol) was dissolved in dry dichloromethane (0.7 mL). PPh_3AuCl (5 mg, 10.2 µmol) and AgOTf (2.6 mg, 10.2 µmol) was added and the reaction mixture was stirred for 48 hours, then filtered through a plug of silica with diethyl ether and concentrated *in vacuo*. Purification by column chromatography (2:1 hexane/dichloromethane to 1:2 hexane/dichloromethane) afforded the title compound as separable diastereoisomers (37 mg, 0.15 mmol, 74%, *cis/trans* 1.7:1).

cis-**2**: white solid; R_f 0.31 (2:1 dichloromethane/hexane); m.p. 91 °C; δ_H (400 MHz, $CDCl_3$) 5.81 (ddd, *J* = 17.3, 10.6, 5.1 Hz, 1H), 5.38 - 5.18 (m, 2H), 4.56 (ddd, *J* = 11.9, 6.4, 2.0 Hz, 1H), 4.31 - 4.17 (m, 1H), 3.98 (d, *J* = 10.3 Hz, 1H), 1.98 - 1.43 (m, 8H), 1.36 - 0.96 (m, 5H); δ_C (101 MHz, $CDCl_3$) 135.3 (CH), 117.3 (CH_2), 88.3 (CH), 56.4 (CH), 42.2 (CH), 32.5 (CH_2), 28.3 (CH_2), 28.0 (CH_2), 26.3 (CH_2), 25.9 (CH_2), 25.7 (CH_2); ν_{max}/cm^{-1} 3276, 2927, 2852, 1650, 1436, 1347, 1175; m/z (ESI^+) 263 ($M + NH_4^+$, 100%), 246 (15%); HRMS (ESI^+) found 263.1428, $C_{11}H_{23}O_3N_2S$ $(M + NH_4)^+$ requires 263.1424.

trans-**2**: colourless oil; R_f 0.15 (2:1 dichloromethane/hexane) δ_H (400 MHz, $CDCl_3$) 6.18 (ddd, *J* = 17.4, 10.7, 5.5 Hz, 1H), 5.28 (ddd, J = 10.7, 1.9, 0.7 Hz, 1H), 5.25 (ddd, *J* = 17.4, 1.8, 0.7 Hz, 1H), 4.67 – 4.56 (m, 1H), 4.48 (d, *J* = 6.6 Hz, 1H), 4.29 - 4.13 (m, 1H), 2.08 – 1.91 (m, 1H), 1.99 - 1.92 (m, 1H), 1.88 (ddd, *J* = 14.5, 3.9, 2.9 Hz, 1H), 1.83 - 1.61 (m, 5H), 1.34 - 0.96 (m, 5H); δ_C (101 MHz, $CDCl_3$) 136.0 (CH), 117.2 (CH_2), 86.3 (CH), 55.3 (CH), 41.7 (CH), 30.4 (CH_2), 28.4 (CH_2), 28.2 (CH_2), 26.3 (CH_2), 25.8 (CH_2), 25.6 (CH_2); ν_{max}/cm^{-1} 3277, 2927, 2854, 1645, 1408, 1361, 1175, 870; m/z (ESI^+) 263 ($M + NH_4^+$, 100%), 246 (15%), 149 (15%); HRMS (ESI^+) found 263.1428, $C_{11}H_{23}O_3N_2S$ $(M + NH_4)^+$ requires 263.1424.

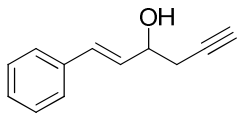
1-Cyclohexylbut-3-yn-1-ol (214)[184]



Under an inert atmosphere (nitrogen), magnesium (1.3 g, 52.8 mmol) was dissolved in dry ether (10 mL). Mercuric chloride (5 mg, 18.4 µmol) and propargyl bromide (80% wt in toluene) (0.2 mL, 0.2 g, 1.8 mmol) was added. The reaction mixture was warmed with stirring until the reaction began, evidenced by the boiling of ether. The reaction mixture was cooled to -25 °C. A solution of cyclohexanecarboxaldehyde **218** (2.7 g, 2.9 mL, 23.8 mmol) and propargyl bromide (80% wt in toluene) (3.3 mL, 4.4 g, 29.6 mmol) dissolved in dry diethyl ether (10 mL) was added dropwise to the flask over 2 hours. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was

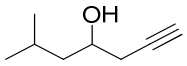
quenched by the addition of ice and saturated ammonium chloride solution. The aqueous layer was separated and further extracted with diethyl ether (2 x 25 mL) and the combined organic phase dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (8:1 petroleum ether/ethyl acetate) afforded the title compound (3.2 g, 21.0 mmol, 88%). δ_H (400 MHz, $CDCl_3$) 3.54-3.44 (m, 1H), 2.50 – 2.32 (m, 3H), 2.09 (dd, *J* = 2.7, 2.7 Hz, 1H), 1.98 – 1.63 (m, 4H), 1.56 – 1.43 (m, 1H), 1.34 – 0.95 (m. 6H); δ_C (75 MHz, $CDCl_3$) 81.3 (C), 74.0 (CH), 70.7 (CH), 42.5 (CH), 29.0 (CH_2), 28.2 (CH_2), 26.4 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 24.6 (CH_2); ν_{max}/cm^{-1} 3309, 2925, 2853, 2250, 1450, 906.

(*E*)-1-Phenylhex-1-en-5-yn-3-ol (220)[185]



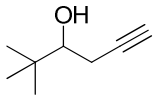
Under an inert atmosphere (nitrogen), to a stirring solution of aluminium (183 mg, 6.8 mmol) in dry tetrahydrofuran (3.5 mL) was added mercuric chloride (few crystals) followed by a solution of propargyl bromide (80% wt in toluene) (1.1 mL, 9.8 mmol) in dry tetrahydrofuran (1.5 mL). The mixture was stirred at 40°C for 30 minutes. *Trans*-cinnamaldehyde **219** (1 g, 7.6 mmol) in dry tetrahydrofuran (1.5 mL) was added and stirred at 40 °C for 30 minutes. The mixture was poured into ice-water (10 mL) and saturated ammonium chloride solution (10 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic layer was washed with brine (10mL) and dried ($MgSO_4$). Purification by column chromatography (6:1 petroleum ether/ethyl acetate) afforded the title compound as a yellow oil (1.1 g, 6.6 mmol, 87%). δ_H (300 MHz, $CDCl_3$) 7.45 – 7.19 (m, 5H), 6.67 (dd, *J* = 15.9, 0.9 Hz, 1H), 6.29 (dd, *J* = 15.9, 6.3 Hz, 1H), 4.52 – 4.46 (m, 1H), 2.68 – 2.45 (m, 2H), 2.12 (s, 1H), 2.09 (dd, *J* = 2.7, 2.7 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 135.3 (C), 130.3 (CH), 129.0 (CH), 127.6 (CH), 126.9 (CH), 125.6 (CH), 79.2 (C), 70.1 (CH), 69.7 (CH), 27.8 (CH_2); ν_{max}/cm^{-1} 3570, 3376, 3271, 2118, 1802, 1591, 1484, 1072.

6-Methylhept-1-yn-4-ol (222)[186]



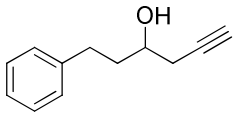
Under an inert atmosphere (nitrogen), magnesium (1.3 g, 52.8 mmol) was dissolved in dry diethyl ether (10 mL). Mercuric chloride (5.3 mg, 19.5 µmol) and propargyl bromide (80% wt in toluene (0.2 mL, 0.2 g, 1.8 mmol) was added. The reaction mixture was warmed with stirring until the reaction began, evidenced by the boiling of ether. The reaction mixture was cooled to -78 °C and a solution of isovaleraldehyde **221** (2.6 mL, 2.1 g, 23.8 mmol) and propargyl bromide (80% wt in toluene) (3.3 mL, 4.4 g, 29.6 mmol) dissolved in dry diethyl ether (10 mL) was added dropwise and stirred for 2 hours before warming to room temperature and stirring for a further 1 hour. The reaction was quenched by the addition of saturated ammonium chloride and the organic phase separated. The aqueous phase was further extracted with diethyl ether (2 x 25 mL) and the combined organic phase dried (Na_2SO_4). Purification by column chromatography (8:1 petroleum ether/ethyl acetate to 1:1 petroleum ether/ethyl acetate) affording the title compound as a yellow oil (1.7 g, 13.7 mmol, 58%). δ_H (300 MHz, $CDCl_3$) 3.85 (m, 1H), 2.43 (ddd, *J* = 16.7, 4.6, 2.6 Hz, 1H), 2.30 (ddd, *J* = 16.7, 6.7, 2.7 Hz, 1H), 2.06 (dd, *J* = 2.7, 2.7 Hz, 1H), 1.87 – 1.83 (m, 1H), 1.78 (m, 1H), 1.49 (m, 1H), 1.32 (m, 1H), 0.94 (d, *J* = 2.4 Hz, 3H), 0.92 (d, *J* = 2.3 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 80.9 (C), 70.8 (CH), 68.0 (CH), 45.4 (CH_2), 27.9 (CH_2), 24.7 (CH), 23.3 (CH_3), 22.1 (CH_3). ν_{max}/cm^{-1} 3311, 2957, 2927, 2869, 1726, 1468, 757.

2,2-Dimethylhex-5-yn-3-ol (224)[187]



Under an inert atmosphere (nitrogen), magnesium (1.3 g, 52.8 mmol) was dissolved in dry diethyl ether (10 mL). Mercuric chloride (5.3 mg, 19.5 µmol) and propargyl bromide (80% wt in toluene (0.2 mL, 0.2 g, 1.8 mmol) were added. The reaction mixture was warmed with stirring until the reaction began, evidenced by the boiling of ether. The reaction mixture was cooled to -25 °C and a solution of pivaldehyde **223** (2.6 mL, 2.1 g, 23.8 mmol) and propargyl bromide (80% wt in toluene) (3.3 mL, 4.4 g, 29.6 mmol) dissolved in dry diethyl ether (10 mL) was added dropwise over a 2 hour period before warming to room temperature and stirring overnight. The reaction was quenched by the pouring into an ice and saturated ammonium chloride solution. The separated aqueous phase was further extracted with diethyl ether (2 x 25 mL) and the combined organic phase dried (Na_2SO_4). Purification by column chromatography (8:1 petroleum ether/ethyl acetate to 1:1 petroleum ether/ethyl acetate) affording the title compound as a yellow oil (1.0 g, 7.9 mmol, 33%). δ_H (300 MHz, $CDCl_3$) 3.51 – 3.39 (m, 1H), 2.44 (m, 1H), 2.25 (m, 1H), 2.12 – 2.01 (m, 2H), 0.92 (s, 9H); δ_H (75 MHz, $CDCl_3$) 82.3 (CH), 77.3 (C), 70.2 (CH), 34.4 (C), 25.4 (CH_2), 20.1 (CH_3); ν_{max}/cm^{-1} 3307, 2954, 2923, 2854, 1719, 1463.

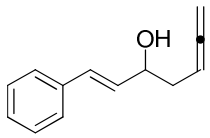
1-Phenylhex-5-yn-3-ol (226)[188]



Magnesium (668 mg, 27.5 mmol) was dissolved in dry diethyl ether (5.5 mL) and mercuric chloride (2.9 mg, 10.7 µmol) was added followed by propargyl bromide (80% wt. in toluene) (0.2 g, 0.2 mL, 2.2 mmol). The reaction was warmed with stirring until the reaction began, as evidenced by the boiling of ether. The reaction mixture was cooled

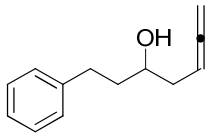
to -25 °C. A solution of hydrocinnamaldehyde **225** (2.3 g, 2.3 mL, 17.2 mmol) and propargyl bromide (80% wt in toluene) (3.1 g, 2.3 mL, 20.2 mmol) in diethyl ether (5.5 mL) was added dropwise over 15 minutes. After 2 hours the flask was warmed to room temperature and stirring continued overnight. The reaction mixture was poured into ice-water and sat ammonium chloride solution was added. The separated aqueous layer was further extracted with diethyl ether (2 x 30 mL), the combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography afforded the title compound as a yellow oil (2.9 g, 16.8 mmol, 98%). δ_H (300 MHz, $CDCl_3$) 7.39 – 7.16 (m, 5H), 3.95 – 3.73 (m, 1H), 2.94 – 2.65 (m, 2H), 2.57 – 2.31 (m, 2H), 2.10 – 2.06 (m, 1H), 1.99 (s, 1H), 1.94 – 1.87 (m, 2H); δc (75 MHz, $CDCl_3$) 141.7 (C), 128.5 (CH), 128.5 (CH), 126.0 (CH), 80.7 (C), 71.0 (C), 69.1 (CH), 37.8 (CH_2), 31.9 (CH_2), 27.5 (CH_2). ν_{max}/cm^{-1} 3386, 3293, 1496, 1455, 1051, 746, 698.

(*E*)-1-Phenylhepta-1,5,6-trien-3-ol (227)[189]



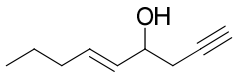
Under an inert atmosphere (nitrogen), (*E*)-1-phenylhex-1-en-5-yn-3-ol **220** (1.0 g, 5.8 mmol), paraformaldehyde (348 mg) and diisopropylamine (1.5 mL, 1.1 g, 10.4 mmol) were dissolved in dry dioxane (13 mL). Copper bromide (250 mg, 2.9 mmol) was added and the reaction mixture refluxed for 2 hours before being filtered through a plug of silica using diethyl ether. Purification by column chromatography (4:1 petroleum ether/ethyl acetate) afforded the desired material as a yellow oil (401 mg, 2.2 mmol, 37%). δ_H (300 MHz, $CDCl_3$) 7.44 – 7.20 (m, 5H), 6.63 (dd, *J* = 15.9, 1.0 Hz, 1H), 6.25 (dd, *J* = 15.9, 6.3 Hz, 1H), 5.24 – 5.08 (m, 1H), 4.79 - 4.75 (m, 2H), 4.49 – 4.30 (m, 1H), 2.42 – 2.27 (m, 2H); δc (75 MHz, $CDCl_3$) 209.6 (C), 136.7 (C), 131.3 (CH), 130.6 (CH), 128.6 (CH), 127.7 (CH), 126.5 (CH), 85.7 (CH), 72.1 (CH), 67.1 (CH_2), 36.7 (CH_2). ν_{max}/cm^{-1} 3374, 3056, 1954, 1598, 1494, 967, 845, 747.

1-Phenylhepta-5,6-dien-3-ol (228)[183]



Under an inert atmosphere (nitrogen), 1-phenylhex-5-yn-3-ol **226** (2.2 g, 12.4 mmol) paraformaldehyde (691 mg) and diisopropylamine were dissolved in dry dioxane (25 mL). Copper(I) bromide (831 mg, 5.8 mmol) was added and the reaction mixture refluxed for 5 hours before being filtered through a plug of silica using diethyl ether. Purification by column chromatography (8:1 petroleum ether/ethyl acetate to 4:1 petroleum ether/ethyl acetate) afforded the desired material as a clear oil (1.0 g, 5.5 mmol, 48%). δ_H (300 MHz, $CDCl_3$) 7.35 – 7.14 (m, 5H), 5.21 – 5.05 (m, 1H), 4.75 – 4.71 (m, 2H), 3.84 – 3.60 (m, 1H), 2.90 – 2.61 (m, 2H), 2.33 – 2.07 (m, 2H), 1.89 – 1.74 (m, 2H), 1.69 (s, 1H); δ_C (75 MHz, $CDCl_3$) 209.4 (C), 142.0 (C), 128.3 (CH),127.8 (CH), 125.7 (CH), 85.8 (CH), 75.3 (CH_2), 70.2 (CH), 38.2 (CH_2), 36.5 (CH_2), 32.1 (CH_2); ν_{max}/cm^{-1} 3384, 3056, 2947, 2855, 1952.

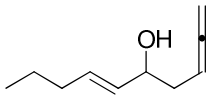
(*E*)-non-5-en-1-yn-4-ol (229)[190]



Under an inert atmosphere (nitrogen), to a stirring solution of aluminium (366 mg, 13.6 mmol) in dry tetrahydrofuran (7.0 mL) was added mercuric chloride (44 mg) followed by a solution of propargyl bromide (80% wt in toluene) (1.7 mL, 15.1 mmol) in dry tetrahydrofuran (3.0 mL). The mixture was stirred at 40 °C for 30 minutes. *Trans*-2-hexen-1-al (1.9 g, 19.7 mmol) in dry tetrahydrofuran (3.0 mL) was added and stirred at 40 °C for 30 minutes. The mixture was poured into ice-water (20 mL) and saturated ammonium chloride solution (20 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic layer was washed with brine (10mL) and dried ($MgSO_4$). Purification

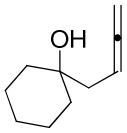
by column chromatography (8:1 petroleum ether/ethyl acetate) afforded the title compound as a colourless oil (900 mg, 6.5 mmol, 43%). δ_H (300 MHz, $CDCl_3$) 5.77 (dtd, *J* = 15.4, 6.7, 0.9 Hz, 1H), 5.57 (ddt, *J* = 15.4, 6.6, 1.3 Hz, 1H), 4.51 – 4.19 (m, 1H), 2.58 – 2.36 (m, 2H), 2.16 – 2.01 (m, 3H), 1.94 (d, *J* = 3.6 Hz, 1H), 1.53 – 1.35 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 133.2 (CH), 130.8 (CH), 80.6 (CH), 77.2 (C), 70.8 (CH), 34.2 (CH_2), 27.7 (CH_2), 22.2 (CH_2), 13.6 (CH_3); ν_{max}/cm^{-1} 3309, 2960, 2929, 2874, 1722, 1458, 1380, 1248, 1098, 1034, 968; m/z (ESI^+) 156 ($M + NH_4^+$, 70%), 138 (M^+, 100%); HRMS (ESI^+) found 156.1384, $C_9H_{18}ON$ $(M + NH_4)^+$ requires 156.1383.

(*E*)-deca-1,2,6-trien-5-ol (230)



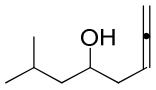
Under an inert atmosphere (nitrogen), (*E*)-non-5-en-1-yn-4-ol **229** (759 mg, 5.5 mmol), paraformaldehyde (330 mg) and diisopropylamine (1.0 g, 1.4 mL, 9.9 mmol) were dissolved in dry dioxane (12 mL). Copper(I) bromide (229 mg, 2.8 mmol) was added and the reaction mixture refluxed for 6 hours. The reaction mixture was filtered through a plug of silica using diethyl ether and concentrated *in vacuo*. Purification by column chromatography (8:1 petroleum ether/ethyl acetate) afforded the title compound as a clear oil (439 mg, 2.9 mmol, 52%). δ_H (400 MHz, $CDCl_3$) 5.69 (dtd, *J* = 15.4, 6.7, 1.1 Hz, 1H), 5.49 (ddt, *J* = 15.4, 6.7, 1.4 Hz, 1H), 5.16 – 5.04 (m, 1H), 4.76 – 4.70 (m, 2H), 4.21 – 4.11 (m, 1H), 2.30 – 2.19 (m, 2H), 2.07 – 1.96 (m, 2H), 1.47 – 1.33 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 209.5 (C), 132.4 (CH), 132.0 (CH), 85.9 (CH), 74.8 (CH_2), 72.2 (CH), 36.7 (CH_2), 34.3 (CH_2), 22.3 (CH_2), 13.6 (CH_3); ν_{max}/cm^{-1} 3315, 2931, 2864, 1948, 1714, 1458, 862; m/z (ESI^+) 152 (M^+, 100%), 135 (30%); HRMS (ESI^+) found 170.1541, $C_{10}H_{20}ON$ $(M + NH_4)^+$ requires 170.1539.

1-(Buta-2,3-dien-1-yl)cyclohexanol (232)[191]



Under an inert atmosphere (nitrogen), 1-(prop-2-yn-1-yl)cyclohexanol **231** (1.2 g, 8.7 mmol), paraformaldehyde (522 mg) and diisopropylamine (1.6 g, 2.2 mL, 15.7 mmol) were dissolved in dry dioxane (19 mL). Copper(I) bromide (362 mg, 4.35 mmol) was added and the reaction mixture refluxed for 6 hours. The reaction mixture was filtered through a plug of silica using diethyl ether and concentrated *in vacuo*. Purification by column chromatography (8:1 petroleum ether/ethyl acetate) afforded the title compound as a white solid (443 mg, 2.9 mmol, 33%). δ_H (400 MHz, $CDCl_3$) 5.22 – 5.12 (m, 1H), 4.72 - 4.68 (m, 2H), 2.17 (ddd, *J* = 8.0, 2.5, 2.5 Hz, 2H), 1.97 – 1.34 (m, 10H); δ_C (100 MHz, $CDCl_3$) 210.0 (C), 84.8 (CH), 73.9 (CH_2), 71.4 (C), 41.6 (CH_2), 37.2 (CH_2), 25.8 (CH_2), 22.2 (CH_2); v_{max}/cm^{-1} 3365, 1953, 1145, 1054, 783, 734.

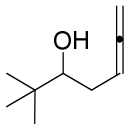
2-Methylocta-6,7-dien-4-ol (233)[192]



Under an inert atmosphere (nitrogen), 6-methylhept-1-yn-4-ol **222** (1.5 g, 11.9 mmol), paraformaldehyde (715 mg) and diisopropylamine (3.0 mL, 2.1 g, 21.4 mmol) were dissolved in dry dioxane (26 mL). Copper bromide (860 mg, 6.0 mmol) was added to the stirring solution and the solution was refluxed for 5 hours before being filtered through a silica plug using diethyl ether. Purification by column chromatography (8:1 petroleum ether/ethyl acetate to ethyl acetate) gave the desired material as a yellow oil (672 mg, 4.8 mmol, 40%). δ_H (400 MHz, $CDCl_3$) 5.20 – 5.08 (m, 1H), 4.76 – 4.70 (m, 2H), 3.85 – 3.71 (m, 1H), 2.28 – 2.04 (m, 2H), 1.87 – 1.72 (m, 1H), 1.46 – 1.42 (m, 1H), 1.30-1.25

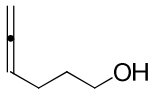
(m, 1H), 0.96 (d, *J* = 4.6 Hz, 3H), 0.95 (d, J = 4.6 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 209.5 (C), 86.3 (CH), 74.9 (CH_2), 69.3 (CH), 46.0 (CH_2), 37.1 (CH_2), 22.2 (CH), 17.6 (CH_3) 17.3 (CH_3); ν_{max}/cm^{-1} 3353, 2956, 2924, 1957, 1468, 1367, 840.8.

2,2-Dimethylhepta-5,6-dien-3-ol (234)[193]



Under an inert atmosphere (nitrogen), 2,2-dimethylhex-5-yn-3-ol (1.0 g, 7.9 mmol), paraformaldehyde (473 mg) and diispropylamine (2.0 mL, 1.4 g, 14.1 mmol) were dissolved in dry dioxane (17 mL). Copper bromide (569 mg, 4.0 mmol) was added and the reaction mixture refluxed for 5 hours. The reaction mixture was flushed through a plug of silica using diethyl ether. Purification by column chromatography (8:1 petroleum ether/ethyl acetate to 2:1 petroleum/ethyl acetate) gave the desired material as a yellow oil (461 mg, 3.3 mmol, 42%). δ_H (400 MHz, $CDCl_3$) 5.24 – 5.12 (m, 1H), 4.78 – 4.69 (m, 2H), 3.30 (ddd, *J* = 10.6, 3.7, 2.1 Hz, 1H), 2.36 – 2.20 (m, 1H), 2.05 – 1.92 (m, 1H), 0.93 (s, 9H); δ_C (75 MHz, $CDCl_3$) 208.7 (CH_2), 87.8 (CH), 74.7 (C), 73.3 (CH), 35.7 (CH_2), 31.2 (C), 20.1 (CH_3); ν_{max}/cm^{-1} 3377, 2959, 2873, 1726, 1657, 1479, 1467, 1366, 1175, 1076.

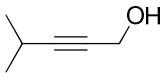
Hexa-4,5,dien-1-ol (236)[194]



Under an inert atmosphere (nitrogen), 4-pentyn-1-ol **235** (1.0 g, 12.0 mmol), paraformaldehyde (714 mg) and diisopropylamine (3.0 mL, 2.2 g, 21.3 mmol) were dissolved in dioxane (23 mL). Copper(I) bromide (500 mg, 6.0 mmol) was added and the reaction mixture refluxed for 6 hours. The room temperature reaction mixture was

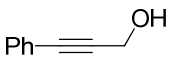
filtered through a plug of silica with diethyl ether and concentrated *in vacuo*. Purification by column chromatography (4:1 petroleum ether/ethyl acetate) afforded the title compound as a clear oil (556 mg, 5.7 mmol, 48%). δ_H (300 MHz, $CDCl_3$) 5.17 – 5.12 (m, 1H), 4.74 – 4.62 (m, 2H), 3.71 – 3.67 (m, 2H), 2.18 – 2.02 (m, 2H), 1.78 – 1.62 (m, 2H), 1.35 (s, 1H); δ_C (75 MHz, $CDCl_3$) 208.5 (C), 89.4 (CH), 75.1 (CH_2), 62.3 (CH_2), 31.9 (CH_2), 24.5 (CH_2); ν_{max}/cm^{-1} 3325, 2938, 1956, 1437, 1169, 1056, 977.

4-Methylpent-2-yn-1-ol (238)[195]



To a solution of 3-methyl-1-butyne **237** (2.5 g, 36.7 mmol, 3.8 mL) in tetrahydrofuran (47 mL) at -78 °C was added a solution of *n*-butyllithium in hexanes (2.5 M; 14.7 mL) over 10 minutes. The reaction mixture was stirred at -78°C for 40 minutes and then paraformaldehyde (1.6 g) was added and the reaction mixture allowed to warm to room temperature and stirred for 18 hours. The reaction mixture was quenched with saturated ammonium chloride solution (2 mL) followed by diethyl ether (57 mL). The mixture was filtered through a plug of celite and dried (Na_2SO_4) affording the desired material as a yellow oil (15% tetrahydrofuran by NMR) (3.5 g, 35.2 mmol, 96% yield). Reacted on crude.

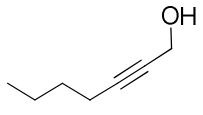
3-Phenylprop-2-yn-1-ol (240)[196]



To a solution of phenylacetylene **239** (3.9 g, 4.1 mL, 38 mmol) in tetrahydrofuran (48 mL) was added at -78 °C a solution of *n*-butyllithium in hexanes (2.5M; 15mL) dropwise over 10 minutes. The reaction mixture was stirred at -78 °C for 40 minutes and then

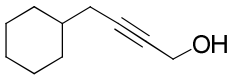
paraformaldehyde (1.6 g) was added and the reaction mixture warmed to room temperature and stirred for 5 hours. The reaction mixture was quenched with saturated ammonium chloride solution (2 mL) followed by diethyl ether (57 mL). The separated aqueous phase was further extracted with diethyl ether and the combined organic phase dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (4:1 petroleum ether/ethyl acetate) afforded the title compound as a yellow oil (3.7 g, 27.7 mmol, 73%). δ_H (300 MHz, $CDCl_3$) 7.42 – 7.32 (m, 2H), 7.31 – 7.19 (m, 3H), 4.44 (d, J = 6.2 Hz, 2H), 1.65 (t, J = 6.2 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 131.7 (CH), 128.5 (CH), 128.3 (CH), 122.5 (C), 87.2 (C), 85.8 (C), 51.7 (CH_2); ν_{max}/cm^{-1} 3311, 2913, 2866, 1489, 1442, 1019.

Hept-2-yn-1-ol (242)[197]



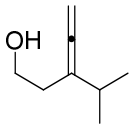
Under an inert atmosphere (nitrogen), to a solution of 1-hexyne **241** (5.4 g, 66.2 mmol) in tetrahydrofuran (40 mL) was added at -78 °C *n*-butyllithium in hexanes (1.3 M; 50 mL) dropwise over 10 minutes. The reaction mixture was stirred for 40 minutes at -78 °C and paraformaldehyde (2.7 g) was added. The reaction mixture was allowed to reach room temperature and stirred for 16 hours. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with diethyl ether (2 x 40 mL) and the combined organic phase was washed with brine (2 x 15 mL) and dried (Na_2SO_4) and concentrated *in vacuo* affording the title compound as a clear oil (6.3 g, 56.2 mmol, 85%). δ_H (300 MHz, $CDCl_3$) 4.31 – 4.19 (m, 2H), 2.28 – 2.10 (m, 2H), 1.57 – 1.19 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 85.3 (C), 78.5 (C), 51.1 (CH_2),31.2 (CH_2), 21.5 (CH_2), 18.8 (CH_2) 13.2 (CH_3); ν_{max}/cm^{-1} 3313, 2958, 2933, 2864, 1137, 1009.

4-Cyclohexylbut-2-yn-1-ol (246)[198]



Under an inert atmosphere (nitrogen), 3-cyclohexyl-1-propyne **245** (3.0 g, 3.6 mL, 24.5 mmol) was dissolved in tetrahydrofuran (30 mL) and n-butyllithium in hexanes (2.0 M; 12.3 mL) was added at -78 °C. The reaction mixture was stirred for 1 hour and then paraformaldehyde (1.0 g) was added. The reaction mixture was warmed to room temperature and stirred for a further 18 hours. The reaction mixture was quenched with saturated ammonium chloride solution (30 mL) and extracted with diethyl ether (2 x 20 mL) and the combined organic phase was washed with brine (2 x 10 mL) and dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (8:1 petroleum ether/ethyl acetate) afforded the title compound as a clear oil (3.2 g, 21.2 mmol, 86%). δ_H (300 MHz, $CDCl_3$) 4.24 (dt, *J* = 5.8, 2.1 Hz, 2H), 2.09 (dt, *J* = 6.7, 2.2 Hz, 2H), 1.91 – 1.52 (m, 4H), 1.52 – 1.33 (m, 1H), 1.33 – 1.07 (m, 4H), 1.07 – 0.44 (m, 2H); δ_C (75 MHz, $CDCl_3$) 85.4 (C), 79.2 (C), 51.4 (CH_2), 37.2 (CH), 32.7 (CH_2), 26.6 (CH_2), 26.2 (CH_2), 26.1 (CH_3); ν_{max}/cm^{-1} 3332, 2921, 2851, 1448, 1136, 1006.

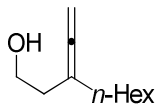
3-Isopropylpenta-3,4-dien-1-ol (249)



Under an inert atmosphere (nitrogen), 4-methylpent-2-yn-1-ol **238** (3.5 g, 35 mmol) was dissolved in triethyl orthoacetate (21 mL, 117 mmol) and propionic acid (0.7 mL, 9.5 mmol) was added. The reaction mixture was heated to reflux once fitted with a Dean-Stark apparatus and refluxed for 5 hours. Purification by distillation gave the desired allenoate (3.8 g, 22.9 mmol, 65%) b.p. 63-67 °C (@10 mmHg). The allenoate (1.9 g, 11.3 mmol) was dissolved in tetrahydrofuran (10 mL) and added dropwise to a solution of

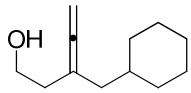
lithium aluminium hydride (566 mg, 14.9 mmol) in tetrahydrofuran (10 mL) at 0 °C and warmed to room temperature and stirred for 2 hours. Following a Fieser work up the reaction mixture was filtered through a plug of silica using diethyl ether and concentrated *in vacuo*. Purification by column chromatography (4:1 petroleum ether/ethyl acetate) afforded the title compound as a clear oil (1.1 g, 8.3 mmol, 72% (over 2 steps). δ_H (300 MHz, $CDCl_3$) 4.79 (dt, *J* = 6.1, 3.0 Hz, 2H), 3.77 – 3.73 (m, 2H), 2.30 – 2.16 (m, 2H), 2.16 – 2.03 (m, 1H), 1.78 – 1.56 (m, 1H), 1.04 (d, *J* = 6.8 Hz, 6H); δ_C (75 MHz, $CDCl_3$) 204.3 (C), 106.7 (C), 77.6 (CH_2), 61.1 (CH_2), 33.3 (CH_2), 30.7 (CH), 21.5 (CH_3); ν_{max}/cm^{-1} 3316, 2962, 2931, 2871, 1953, 1465, 1041, 844; m/z (ESI^+) 127 ($M + H^+$, 100%), 110 (30%), 109 (35%); HRMS (ESI^+) found 126.1038, $C_8H_{14}O$ (M^+) requires 126.1039.

3-Vinylidenenonan-1-ol (251)[64]



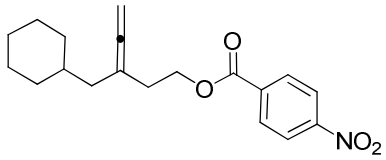
Non-2-yn-1-ol **250** (3.0 g, 21.4 mmol) was dissolved in triethyl orthoacetate (12.8 mL, 71.2 mmol) and propionic acid (0.4 mL, 5.8 mmol) was added. The reaction mixture was refluxed for 8 hours. Propionic acid (0.4 mL, 5.8 mmol) was added and the reaction mixture refluxed for a further 8 hours. Propionic acid (0.4, 5.8 mmol) was added and the reaction mixture refluxed for a further 8 hours. Purification by column chromatography (8:1 petroleum ether/ethyl acetate) afforded the crude allenoate (3.8 g). The allenoate (3.8 g) was dissolved in dry tetrahydrofuran (18 mL) and this solution was added dropwise to lithium aluminium hydride (952 mg, 25.1 mmol) in tetrahydrofuran (10 mL) at 0 °C and stirred at room temperature for 23 hours. Following a Fieser work up, filtration to remove lithium salts and purification by column chromatography (6:1 petroleum ether/ethyl acetate) afforded the title compound as a colourless oil (1.4 g, 8.2 mmol, 38%). δ_H (300 MHz, $CDCl_3$) 4.78 – 4.67 (m, 2H), 3.74 (t, *J* = 6.1 Hz, 2H), 2.20 (tt, *J* = 6.3, 3.2 Hz, 2H), 2.15 – 1.91 (m, 2H), 1.71 (s, 1H), 1.48 – 1.03 (m, 8H), 0.87 (t, *J* = 6.8 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 205.5 (C), 100.3 (C), 76.2 (CH_2), 60.8 (CH_2), 35.3 (CH_2), 32.3 (CH_2), 31.7 (CH_2), 29.1 (CH_2), 27.4 (CH_2), 22.6 (CH_2), 14.1(CH_3); ν_{max}/cm^{-1} 3336, 2956, 2925, 2857, 1957, 1045, 851, 724.

3-(Cyclohexylmethyl)penta-3,4-dien-1-ol (252)



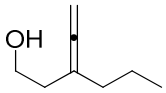
4-Cyclohexylbut-2-yn-1-ol **246** (2.6 g, 17.1 mmol) was dissolved in triethyl orthoacetate (10.0 mL, 56.4 mmol) and propionic acid (0.3 mL, 4.5 mmol) was added. The reaction mixture was refluxed for 24 hours. Propionic acid (0.3 mL, 4.5 mL) was added and the reaction mixture refluxed for a further 24 hours. Propionic acid (0.3 mL) was added and the reaction mixture refluxed for a further 36 hours. Purification by column chromatography (8:1 petroleum ether/ethyl acetate) afforded the crude allenoate (3.6 g). The allenoate (3.6 g) was dissolved in dry tetrahydrofuran (16 mL) and this solution was added dropwise to lithium aluminium hydride (861 mg, 22.7 mmol) in tetrahydrofuran (9 mL) at 0 °C and stirred at room temperature overnight. Following a Fieser work up, filtration to remove lithium salts and purification by column chromatography (6:1 petroleum ether/ethyl acetate) afforded the title compound as a clear oil (2.0 g, 11.3 mmol, 66%). δ_H (300 MHz, $CDCl_3$) 4.75 – 4.69 (m, 2H), 3.74 (dd, *J* = 11.1, 5.6 Hz, 2H), 2.25 – 2.12 (m, 2H), 1.90 – 1.71 (m, 2H), 1.70 – 1.58 (m, 4H), 1.53 – 1.32 (m, 1H), 1.31 – 1.09 (m, 4H), 1.07 – 0.75 (m, 2H); ν_{max}/cm^{-1} 3326, 2920, 2850, 1957, 1448, 1045, 1015, 842. Further characterised by preparation of the 4-nitrobenzoate ester due to instability.

3-(Cyclohexylmethyl)penta-3,4-dien-1-yl 4-nitrobenzoate ester



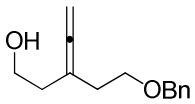
To a solution of 3-(cyclohexylmethyl)penta-3,4-dien-1-ol **252** (108 mg, 0.6 mmol) in dichloromethane (1 mL) was added triethylamine (85 mg, 0.8 mmol) and dimethylaminopyridine (6.8 mg, 56 µmol). To the stirring solution at 0 °C was added *p*-nitro benzoylchloride (128 mg, 0.7 mmol) in dichloromethane (1 mL) drop wise and stirred for 30 minutes. The reaction mixture was stirred at room temperature for 18 hours. Water (10 mL) was added. The separated organic layer was washed with hydrochloric acid (10%; 2 x 1 mL), water (5 mL) then brine (5 mL) and dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (20:1 petroleum ether/ethyl acetate) afforded the title compound as a colourless oil (140 mg, 0.4 mmol, 76%). δ_H (300 MHz, $CDCl_3$) 8.33 – 8.22 (m, 2H), 8.22 – 8.14 (m, 2H), 4.65 (p, *J* = 3.0 Hz, 2H), 4.45 (t, *J* = 6.8 Hz, 2H), 2.39 (tt, *J* = 6.7, 3.2 Hz, 2H), 1.89 (dt, *J* = 6.7, 2.7 Hz, 2H), 1.80 – 1.54 (m, 4H), 1.32 – 1.06 (m, 4H), 1.00 – 0.76 (m, 3H); δ_C (75 MHz, $CDCl_3$) 206.3 (C), 164.6 (C), 150.5 (C), 135.8 (C), 130.7 (CH), 123.5 (CH), 97.4 (C), 75.7 (CH_2), 64.1 (CH_2), 40.5 (CH_2), 35.9 (CH), 33.3 (CH_2), 31.0 (CH_2), 26.5 (CH_2), 26.2 (CH_2); ν_{max}/cm^{-1} 2922, 2850, 1957, 1724, 1527, 1347, 1268, 842; m/z (ESI^+) 347 ($M + NH_4^+$, 100%); HRMS (ESI^+) found 347.1963, $C_{19}H_{27}O_4N_2$ $(M + NH_4)^+$ requires 347.1965.

3-Vinylidenehexan-1-ol (254)[64]



Under an inert atmosphere (nitrogen), 2-hexyn-1-ol **253** (5 g, 51 mmol) was dissolved in triethyl orthoacetate (29.5 mL, 163 mmol) and propionic acid (0.9 mL) was added. The mixture was heated to reflux once fitted with a Dean-Stark apparatus and refluxed for 21 hours. Propionic acid (0.9 mL) was added and the reaction mixture was heated at reflux for a further 19 hours. Propionic acid (0.9 mL) was added and the reaction mixture heated to reflux for a further 24 hours. The crude reaction mixture was filtered through a plug of silica using diethyl ether and concentrated *in vacuo*. The crude allenoate was dissolved in tetrahydrofuran (40 mL) and this was added to lithium aluminium hydride (2.5 g, 66.3 mmol) in tetrahydrofuran (40 mL) at 0 °C. The reaction mixture was stirred overnight and quenched with distilled water (7.5 mL) and stirred for 1 hour. The lithium salts were filtered off and the solution concentrated *in vacuo*. Purification by column chromatography (5:1 petroleum ether/ethyl acetate) afforded the title compound as a clear oil (2.6g, 20.3 mmol, 40%). δ_H (300 MHz, $CDCl_3$) 4.82 – 4.71 (m, 2H), 3.87 – 3.69 (m, 2H), 2.26 – 2.22 (m, 2H), 1.99 – 1.95 (m, 2H), 1.59 – 1.40 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 204.4 (C), 103.2 (C), 76.3 (CH_2), 58.4 (CH_2) 36.7 (CH_2), 32.6 (CH_2), 23.1 (CH_2), 14.3 (CH_3); ν_{max}/cm^{-1} 3377, 2960, 2933, 2869, 1714, 1450, 1378, 1182, 1042.

(3-(2-(Benzyloxy)ethyl)penta-3,4-dien-1-ol (255)

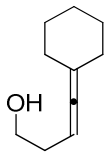


Under an inert atmosphere (nitrogen), at -78 °C, to a solution of ((but-3-yn-1-yloxy)methyl)benzene (10.5 g, 65.5 mmol) in dry tetrahydrofuran (83 mL) was added *n*-

butyllithium in hexanes (1.9 M, 34.5 mL, 65.5 mmol) over 10 minutes. The mixture was stirred for a further 30 minutes. Paraformaldehyde (2.8 g) was added and the reaction mixture was allowed to warm to room temperature and stirred for 19 hours. Saturated ammonium chloride solution (6 mL) was added folowed by diethyl ether (50 mL). The reaction mixture was filtered through a plug of silica with ether. The separated aqueous layer was further extracted with diethyl ether and the combined organic phases were washed with brine and dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (7:3 petroleum ether/ethyl acetate) gave 5-(benzyloxy)pent-2-yn-1-ol **248** as a colourless oil (6.2 g, 32.4 mmol, 50%). This was reacted on below.

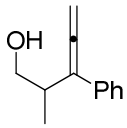
5-(Benzyloxy)pent-2-yn-1-ol **248** (5.0 g, 26.0 mmol) was dissolved in triethyl orthoacetate (15 mL) and propionic acid (0.5 mL) and the reaction mixture refluxed under Dean-Stark conditions for 17 hours. Propionic acid (0.5 mL) was added and refluxed for a further 17 hours. Propionic acid (0.5 mL) was added and the reaction mixture refluxed for a further 17 hours. Purification by column chromatography (16:1 petroleum ether/ethyl acetate to 6:1 petroleum ether/ethyl acetate) afforded the crude allenoate. The allenoate (3.6 g) was dissolved in dry tetrahydrofuran (13 mL) and added dropwise to a solution of lithium aluminium hydride (686 mg, 18.0 mmol) in dry tetrahydrofuran (6 mL) at 0 °C and warmed to room temperature and stirred for 27 hours. Following a Fieser work up the reaction mixture was filtered. The separated aqueous phase was extracted with diethyl ether, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (3:1 petroleum ether/ethyl acetate) afforded the title compound as a colourless oil (2.4 g, 11 mmol, 42% (over 2 steps)). δ_H (300 MHz, $CDCl_3$) 7.39 – 7.25 (m, 5H), 4.79 – 4.74(m, 2H), 4.52 (s, 2H), 3.78 – 3.72 (m, 2H), 3.60 (t, J = 6.6 Hz, 2H), 2.30 (td, J = 6.6 Hz, 3.3 Hz, 2H), 2.24 (td, J = 6.1, 3.0 Hz); δ_C (75 MHz, $CDCl_3$) 206.0 (C), 134.6 (C), 129.1 (CH), 128.5 (CH), 127.9 (CH), 97.5 (C), 77.4 (CH_2), 73.2 (CH_2), 68.7 (CH_2), 60.8 (CH_2), 35.7 (CH_2), 32.3 (CH_2); ν_{max}/cm^{-1} 3406, 2927, 2881, 1715, 1453,1273, 713; m/z (ESI^+) 219 ($M + H^+$, 30%), 213 (100%), 197 (50%), 195 (95%); HRMS (ESI^+) found 437.2683, $C_{28}H_{37}O_4$ $(2M + H)^+$ requires 437.2686.

4-Cyclohexylidenebut-3-en-1-ol (257)[199]



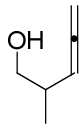
Under an inert atmosphere, 1-ethynylcyclohexanol **256** (5.65 mL, 43 mmol) was dissolved in triethyl orthoacetate (25 mL, 14 mmol) and propionic acid (1.0 mL, 13 mmol) was added. The reaction mixture was refluxed overnight with Dean-Stark apparatus. Propionic acid (1.0 mL, 13 mmol) was added and the reaction refluxed for a further 2 days and concentrated *in vacuo*. Purification by column chromatography (98:2 petroleum ether/ethyl acetate) afforded the crude allenoate (2.3 g, 11.8 mmol, 27%). Under an inert atmosphere (nitrogen), the allenoate (1.0 g, 5.2 mmol) dissolved in dry tetrahydrofuran (5 mL) was added dropwise to a solution of lithium aluminium hydride (254 mg, 6.7 mmol) in tetrahydrofuran (5 mL) and the reaction mixture was stirred for 2 hours. The reaction was quenched with water and then diethyl ether was added. The solution was filtered and the phases separated. The organic layer was washed with water then brine and dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound as a colourless oil (600 mg, 3.9 mmol, 21% (over 2 steps)). δ_H (300 MHz, $CDCl_3$) 5.04 – 4.89 (m, 1H), 3.77 – 3.45 (m, 2H), 2.25 – 2.21 (m, 2H), 2.17 – 2.06 (m, 4H), 1.89 – 1.27 (m, 6H); δ_C (75 MHz, $CDCl_3$) 198.6 (C), 103.0 (C), 84.2 (CH), 61.8 (CH_2), 32.5 (CH_2), 31.4 (CH_2), 27.2 (CH_2), 25.8 (CH_2); ν_{max}/cm^{-1} 3342, 2923, 2850, 1961, 1445, 1339, 1174.

2-Methyl-3-phenylpenta-3,4-dien-1-ol (258)[108]



3-Phenylprop-2-yn-1-ol **240** (2.5 g, 18.9 mmol) was dissolved in triethyl orthopropionate (14 mL, 70 mmol) and propionic acid (0.23 mL) was added. The reaction mixture was stirred at 140 °C for 7 hours fitted with a Dean-Stark apparatus. The reaction mixture was filtered through a plug of silica using a 2:1 mixture of petroleum ether/ethyl acetate giving the crude allenoate (2.6 g). The crude allenoate was added to DIBAL in tetrahydrofuran (1 M; 22.8 mL) at -78 °C whilst stirring and the reaction mixture warmed to room temperature and stirred overnight. Following a Fieser work up, the reaction mixture was diluted with diethyl ether. The separated aqueous phase was further extracted with diethyl ether and the combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (4:1 petroleum ether/ethyl acetate) afforded the title compound as a clear oil (1.6 g, 9.2 mmol, 48% (over 2 steps)). δ_H (300 MHz, $CDCl_3$) 7.50 – 7.09 (m, 5H), 5.27 – 5.10 (m, 2H), 3.76 (dd, *J* = 10.8, 6.2 Hz, 1H), 3.64 (dd, *J* = 10.8, 5.8 Hz, 1H), 3.28 – 2.86 (m, 1H), 1.60 (s, 1H), 1.21 (d, *J* = 6.8 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 207.7 (C), 135.8 (C), 128.5 (CH), 126.9 (CH), 126.4 (CH), 108.0 (C), 79.7 (CH_2), 66.8 (CH_2), 35.8 (CH), 16.8 (CH_3); ν_{max}/cm^{-1} 3437, 2971, 2933, 2877, 1732, 1683, 1449, 1240, 1215, 699.

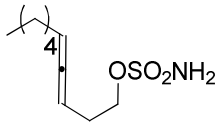
2-Methylpenta-3,4-dien-1-ol (260)[200]



Propargyl alcohol **259** (4.9 mL, 4.7 g, 83.7 mmol) was dissolved in triethyl orthopropionate (30 mL, 150 mmol). The flask was fitted with a Dean-Stark apparatus.

Propionic acid (0.75 mL) was added and the reaction mixture heated at 140 °C for 24 hours and cooled to room temperature. The crude mixture was flushed through a silica plug with diethyl ether and and concentrated *in vacuo*. Purification by column chromatography (16:1 petroleum ether/ethyl acetate) afforded the crude allenoate. The crude allenoate (9.7 g) was dissolved in tetrahydrofuran (30 mL) and this was added dropwise to a suspension of lithium aluminium hydride (3.4 g, 1.3eq) in tetrahydrofuran (10 mL) at 0 °C and warmed to room temperature and stirred for 14 hours. Fieser work up, followed by filtration to remove lithium salts. The reaction mixture was extracted with diethyl ether and dried (Na_2SO_4) and concentrated *in vacuo.* Purification by column chromatography (4:1 petroleum ether/ethyl acetate) afforded the desired material as a clear oil (3.9 g, 40.0 mmol, 47%). δ_H (300 MHz, $CDCl_3$) 5.20 – 5.07 (m, 1H), 4.84 – 4.74 (m, 2H), 3.63 – 3.26 (m, 2H), 2.51 – 2.12 (m, 1H), 1.04 (d, *J* = 6.9 Hz, 3H); δ_C (75MHz, $CDCl_3$) 207.5 (C), 99.0 (CH), 74.2 (CH_2), 64.8 (CH_2), 38.3 (CH), 13.3 (CH_3); ν_{max}/cm^{-1} 3344, 1950, 1472, 1146, 1029.

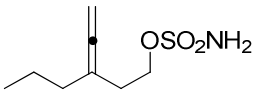
Deca-3,4-dien-1-yl sulfamate (263)



Under an inert atmosphere (nitrogen), formic acid (75 µL, 2.0 mmol) was added dropwise to neat chlorosulfonyl isocyanate (0.2 mL, 2.0 mmol) at 0 °C with rapid stirring. The resulting suspension was stirred at room temperature for 18 hours. The reaction mixture was cooled to 0 °C and dimethylacetamide (0.4 mL) was added and the solution was stirred for 5 minutes. A solution of deca-3,4-dien-1-ol **262** (200 mg, 1.3 mmol) in dimethylacetamide (0.7 mL) was added dropwise and the resulting solution allowed to reach room temperature and stirring was continued for 4 hours. The reaction was quenched by the addition of ethyl acetate (1.8 mL) and brine (1 mL). The reaction mixture was poured into ethyl acetate (3.5 mL) and water (1.5 mL). The separated aqueous phase was further extracted with ethyl acetate (5 mL). The combined organic extracts were washed with brine (2 x 5 mL), dried (Na_2SO_4) and concentrated *in vacuo*.

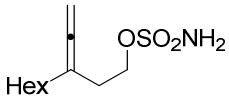
Purification by column chromatography (7:3 petroleum ether/ethyl acetate) afforded the title compound as a colourless oil (195 mg, 0.8 mmol, 62%). δ_H (300 MHz, $CDCl_3$) 5.25 – 5.00 (m, 2H), 4.71 (s, 2H), 4.26 (t, *J* = 6.9 Hz, 2H), 2.48 – 2.42 (m, 2H), 2.01 – 1.93 (m, 2H), 1.58 – 1.21 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 204.7 (C), 92.5 (CH), 85.5 (CH), 70.5 (CH_2), 31.3 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 22.5 (CH_2), 14.1 (CH_3); m/z (ESI^+) 256 ($M + Na^+$, 80%), 251 ($M + NH_4^+$, 100%); HRMS (ESI^+) found 251.1429, $C_{10}H_{23}O_3N_2S$ $(M + NH_4)^+$ requires 251.1424.

3-Vinylidenehexyl sulfamate (264)[79]



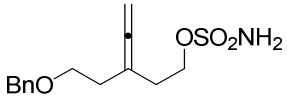
Formic acid (0.8 mL, 20.0 mmol) was added dropwise to chlorosulfonyl isocyanate (1.8 mL, 20.0 mmol) at 0 °C with vigorous stirring. Acetonitrile (3.6 mL) was added and the reaction mixture stirred overnight. A solution of 3-vinylidenehexan-1-ol **254** (1.0 g, 8.0 mmol) in dimethylacetamide (3 mL) was added dropwise at 0 °C and stirred for 20 hours. The reaction mixture was quenched with ethyl acetate (7 mL) and brine (3.5 mL) before being poured onto ethyl acetate (14 mL) and water (5 mL). The separated aqueous layer was extracted with ethyl acetate (10 mL) and the combined organic phase washed with brine (2 x 5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (4:1 petroleum ether/ethyl acetate) afforded the title compound as a yellow oil (701 mg, 3.4 mmol, 43%). δ_H (300 MHz, $CDCl_3$) 4.75 (p, *J* = 3.3 Hz, 2H), 4.67 (br s, 2H), 4.30 (t, *J* = 7.1 Hz, 2H), 2.45 – 2.32 (m, 2H), 2.02 – 1.88 (m, 2H), 1.55 – 1.36 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); δ_C 75 MHz, $CDCl_3$) 205.3 (C), 98.4 (C), 77.6 (CH_2), 68.8 (CH_2), 33.1 (CH_2), 31.6 (CH_2), 29.6 (CH_2), 14.7 (CH_3); ν_{max}/cm^{-1} 3286, 2956, 1959, 1359, 1126.

3-Vinylidenenonyl sulfamate (265)



Under an inert atmosphere (nitrogen), formic acid (0.7 mL, 17.9 mmol) was added drop wise to neat chlorosulfonyl isocyanate (1.6 mL, 17.9 mmol) at 0 °C with vigorous stirring. Acetonitrile (10 mL) was added and the reaction mixture stirred for 18 hours. 3-vinylidenenonan-1-ol **251** (1.3 g, 7.8 mmol) in dimethylacetamide (5 mL) was added drop wise at 0 °C and stirred for 36 hours. The reaction mixture was diluted using ethyl acetate (28 mL) and quenched with brine (14 mL). The mixture was poured into a solution of ethyl acetate (28 mL) and water (10 mL). The separated aqueous phase was further extracted with ethyl acetate (20 mL). The combined organic phase was washed with brine (2 x 5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (3:1 petroleum ether/ethyl acetate) afforded the title compound as a colourless oil (1.3 g, 5.1 mmol, 43%). δ_H (300 MHz, $CDCl_3$) 4.86 – 4.64 (m, 2H), 4.75 (s, 2H), 4.30 (t, *J* = 7.1 Hz, 2H), 2.38 (tt, *J* = 6.9, 3.3 Hz, 2H), 2.03 – 1.89 (m, 2H), 1.70 – 1.19 (m, 8H), 0.91 (t, *J* = 4.7 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 205.5 (C), 98.7 (C), 77.2 (CH_2), 69.5 (CH_2), 32.3 (CH_2), 31.7 (CH_2), 31.0 (CH_2), 28.9 (CH_2), 27.3 (CH_2), 22.6 (CH_2), 14.1 (CH_3); ν_{max}/cm^{-1} 3283, 2957, 2927, 2858, 1958, 1724, 1361, 1125; m/z (ESI^+) 265 (M + NH_4^+, 100%), 255 (15%); HRMS (ESI^+) found 265.1584, $C_{11}H_{25}O_3N_2S$ (M + NH_4)$^+$ requires 265.1580.

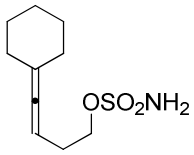
3-(2-(Benzyloxy)ethyl)penta-3,4-dien-1-yl sulfamate (266)



Under an inert atmosphere (nitrogen), formic acid (0.4 mL, 11.5 mmol) was added drop wise to neat chlorosulfonyl isocyanate (1.0 mL, 11.5 mmol) at 0 °C with vigorous

stirring. Acetonitrile (3.6 mL) was added and the reaction mixture stirred for 17 hours. A solution of (3-(2-(benzyloxy)ethyl)penta-3,4-dien-1-ol **255** (1.0 g, 4.6 mmol) in dimethylacetamide (9 mL) was added drop wise at 0 °C and the reaction mixture allowed to reach room temperature and the reaction mixture stirred for 24 hours. The reaction mixture was quenched by the addition of diethyl ether (7 mL) and brine (4 mL). The reaction mixture was poured into diethyl ether (10 mL) and water (7 mL). The separated aqueous layer was further extracted with diethyl ether (10 mL) and the combined organic layer was washed with brine (2 x 5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (19:1 dichloromethane/ethyl acetate) afforded the title compound as a white solid (609 mg, 2.0 mmol, 45%). δ_H (300 MHz, $CDCl_3$) 7.44 – 7.20 (m, 5H), 4.93 – 4.63 (m, 4H), 4.53 (s, 2H), 4.33 (t, J = 6.8 Hz, 2H), 3.63 (t, J = 6.4 Hz, 2H), 2.44 (tt, J = 6.6, 3.2 Hz, 2H), 2.33 (tt, J = 6.4, 3.2 Hz, 2H); δ_C (100 MHz, $CDCl_3$) 205.6 (C), 161.0 (C), 129.6 (CH), 128.4 (CH), 127.7 (CH), 127.6 (CH), 77.2 (CH_2), 73.0 (CH_2), 68.5 (CH_2), 62.1 (CH_2), 32.4 (CH_2), 31.1 (CH_2); ν_{max}/cm^{-1} 3280, 2866, 1958, 1716, 1363, 1176; m/z (ESI^+) 315 ($M + NH_4^+$, 100%), 298 ($M + H^+$, 35%); HRMS (ESI^+) found 298.1115, $C_{14}H_{20}O_4NS$ $(M + H)^+$ requires 298.1108.

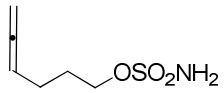
4-Cyclohexylidene-3-en-1-yl sulfamate (267)



Under an inert atmosphere (nitrogen), formic acid (0.2 mL, 6.1 mmol) was added dropwise to neat chlorosulfonyl isocyanate (0.5 mL, 0.9 g, 6.1 mmol) at 0 °C with rapid stirring. The resulting suspension was stirred at room temperature for 18 hours. The reaction mixture was cooled to 0 °C and dimethylacetamide (1.1 mL) was added and the solution stirred for 5 minutes. A solution of 4-cyclohexylidenebut-3-en-1-ol **257** (500 mg, 3.3 mmol) in dimethylacetamide (2.2 mL) was added dropwise was added to the reaction mixture and stirring continued for 5 hours. The reaction mixture was quenched by the addition of ethyl acetate (10 mL) and brine (10 mL). The mixture was poured into ethyl acetate (5 mL) and water (5 mL). The combined organic phase was washed with

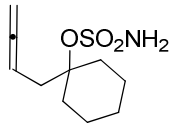
brine (2 x 5 mL) and dried Na_2SO_4 and concentrated *in vacuo* giving the desired material as a clear oil (429 mg, 1.9 mmol, 58%). δ_H (300 MHz, $CDCl_3$) 5.10 – 4.85 (m, 1H), 4.68 (s, 2H), 4.25 (t, *J* = 6.9 Hz, 2H), 2.41 (dd, *J* = 13.3, 6.9 Hz, 2H), 2.17 – 2.05 (m, 4H), 1.69 – 1.35 (m, 6H); δ_C (75 MHz, $CDCl_3$) 199.3 (C), 104.0 (C), 83.2 (CH), 70.8 (CH_2), 31.5 (CH_2), 28.9 (CH_2), 27.3 (CH_2), 26.0 (CH_2); ν_{max}/cm^{-1} 3385, 3282, 2925, 2853, 1966, 1554, 1446, 1359, 1266, 1239, 1175, 978, 924, 851, 825, 797, 739; m/z (ESI^+) 249 ($M + NH_4^+$, 100%), 232 ($M + H^+$, 40%); HRMS (ESI^+) found 232.1004, $C_{10}H_{18}O_3NS$ $(M + H)^+$ requires 232.1002.

Hexa-4,5-dien-1-yl sulfamate (272)



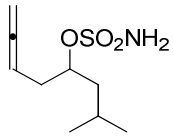
Formic acid was (0.3 mL, 7.8 mmol) was added dropwise to neat chlorosulfonyl isocyanate (0.7 mL, 7.8 mmol) at 0 °C with rapid stirring. The resulting suspension was stirred at room temperature for 18 hours. The reaction mixture was cooled to 0 °C and dimethylacetamide (1.4 mL) was added and the solution stirred for 5 minutes. A solution of hexa-4,5-dien-1-ol **236** (510 mg, 5.2 mmol) in dimethylacetamide (1.4 mL) was added and the resulting solution was warmed to room temperature and stirring continued for 4 hours. The reaction mixture was quenched by the addition of ethyl acetate (7.5 mL) and brine (5 mL). This was poured into ethyl acetate (25 mL) and water (10 mL). The separated aqueous phase was further extracted with ethyl acetate (2 x 25 mL.) The combined organic phase was washed with brine (2 x 5 mL) and dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (4:1 petroleum ether/ethyl acetate) afforded the title compound as a clear oil (445 mg, 2.5 mmol, 48%). δ_H (300 MHz, $CDCl_3$) 5.16 – 5.12 (m, 1H), 4.92 – 4.66 (m, 4H), 4.26 (t, *J* = 6.4 Hz, 2H), 2.22 – 2.06 (m, 2H), 1.97 – 1.81 (m, 2H); δ_C (75 MHz, $CDCl_3$) 208.6 (C), 88.5 (CH), 75.7 (CH_2), 70.7 (CH_2), 27.9 (CH_2), 23.9 (CH_2); ν_{max}/cm^{-1} 3391, 3291, 2939, 1958, 1539, 1455, 1344, 1169, 895; m/z (ESI^+) 178 ($M + H^+$, 100%), 154 (10%), 115 (10%); HRMS (ESI^+) found 178.0533, $C_6H_{12}O_3NS$ $(M + H)^+$ requires 178.0533.

1-(Buta-2,3-dien-1-yl)cyclohexyl sulfamate (274)



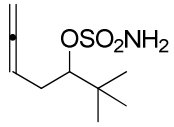
Under an inert atmosphere (nitrogen), formic acid (0.33 mL, 4.0 mmol) was added dropwise to a neat chlorosulfonyl isocyanate (0.74 mL, 4.0 mmol) at 0 ^{o}C with rapid stirring. The resulting suspension was stirred at room temperature for 16 hr. The reaction mixture was cooled to 0 ^{o}C and DMA (1.4 mL) was added and the solution stirred for 5 minutes. Half of this solution was placed in a dry flask and a solution of 1-(buta-2,3-dien-1-yl)cyclohexanol **232** (274 mg, 1.80 mmol) in DMA (0.7 mL) was added dropwise at 0 ^{o}C to the stirring solution. The reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was quenched by the addition of ethyl acetate (1 mL) and brine (1 mL). This was poured into ethyl acetate (3 mL) and water (1 mL). The separated aqueous phase was further extracted with ethyl acetate (2 x 5 mL) and the combined organic phase washed with brine (2 x 2.5 mL), dried Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (petroleum ether) gave the desired material as a clear oil (123 mg, 0.53 mmol, 29%). δ_H (300 MHz, $CDCl_3$) 5.48 (ddd, *J* = 5.1, 3.5, 1.4 Hz, 1H), 5.16 – 4.99 (m, 1H), 4.66 (dt, *J* = 6.6, 2.8 Hz, 2H), 2.64 (d, *J* = 8.6 Hz, 2H), 1.98 (dt, *J* = 12.9, 4.7 Hz, 4H), 1.71 – 1.47 (m, 5H); δ_C (75 MHz, $CDCl_3$) 208.9 (C), 136.3 (C), 121.9 (CH), 88.4 (CH_2), 74.3 (CH_2), 37.4 (CH_2), 28.2 (CH_2), 25.2 (CH_2), 22.9 (CH_2), 22.5 (CH_2); ν_{max}/cm^{-1} 3277, 2927, 2854, 1645, 1408, 1361, 1175, 870; m/z (ESI$^+$) 249 (M+NH_4^+, 100%), 244 (70%); HRMS (ESI$^+$) found 249.0774, $C_{10}H_{21}O_3N_2S$ (M^+) requires 249.0779.

2-Methylocta-6,7-dien-4-yl sulfamate (275)



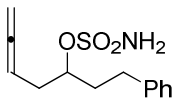
Under an inert atmosphere (nitrogen), formic acid (0.26 mL) was added dropwise to chlorosulfonyl isocyanate (0.6 mL, 6.8 mmol) with vigorous stirring at 0 °C. Acetonitrile (1.2 mL) was added and the reaction mixture stirred overnight. 2-methylocta-6,7-dien-4-ol **233** (378 mg, 2.7 mmol) was added in dimethylacetamide (1.2 mL) and the reaction mixture stirred at room temperature for 24 hours. The reaction mixture was diluted with diethyl ether (4 mL) and quenched with saturated sodium chloride solution (2 mL). This was added to a mixture of diethyl ether (4 mL) and water (3 mL). The separated aqueous phase was further extracted with diethyl ether (3 mL). The combined organic phase washed with saturated sodium chloride solution (2 x 1.5 mL), dried Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (6:1 petroleum ether/ethyl acetate) afforded the title compound as a yellow oil (421 mg, 1.9 mmol, 71%). δ_H (300 MHz, $CDCl_3$) 5.16 – 5.10 (m, 1H), 4.86 – 4.39 (m, 4H), 2.58 – 2.42 (m, 2H), 1.88 – 1.66 (m, 2H), 1.61 – 1.38 (m, 1H), 0.96 (d, *J* = 6.2 Hz, 3H), 0.94 (d, *J* = 6.3 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 209.7 (C), 84.6 (CH_2), 82.7 (CH_2), 75.3 (CH), 42.8 (CH), 33.8 (CH), 24.3 (CH_2), 22.9 (CH_3), 22.2 (CH_3); ν_{max}/cm^{-1} 3362, 3283, 2951, 2935, 1957, 1539, 1351, 1329, 1178; m/z (ESI^+) 218 ($M - H^+$, 100%); HRMS (ESI^+) found 218.0852, $C_9H_{16}O_3NS$ $(M - H)^+$ requires 218.0856.

2,2-Dimethylhepta-5,6-dien-3-yl sulfamate (276)



Under an inert atmosphere (nitrogen), formic acid (0.26 mL) was added dropwise to chlorosulfonyl isocyanate (0.6 mL, 6.8 mmol) with vigorous stirring at 0 °C. Acetonitrile (1.2 mL) was added and the reaction mixture stirred overnight. 2,2-dimethylhepta-5,6-dien-3-ol **234** (415 mg, 2.9 mmol) was added in dimethylacetamide (1.2 mL) and the reaction mixture stirred at room temperature for 24 hours. The reaction mixture was diluted with diethyl ether (4 mL) and quenched with saturated sodium chloride solution (2 mL). This was added to a mixture of diethyl ether (4 mL) and water (3 mL). The separated aqueous phase was further extracted with diethyl ether (3 mL). The combined organic phase washed with saturated sodium chloride solution (2 x 1.5 mL), dried Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (8:1 petroleum ether/ethyl acetate to 2:1 petroleum ether/ ethyl acetate) afforded the title compound as a yellow oil (257 mg, 1.2 mmol, 41%). δ_H (300 MHz, $CDCl_3$) 5.32 – 5.26 (m, 1H), 4.86 – 4.62 (m, 2H), 4.47 – 4.43 (m, 1H), 2.62 – 2.31 (m, 2H), 1.03 (s, 9H); δ_C (75 MHz, $CDCl_3$) 209.2 (C), 92.6 (CH), 87.4 (CH), 75.6 (CH_2), 35.4 (C), 30.4 (CH_2), 26.1 (CH_3); ν_{max}/cm^{-1} 3381, 2964, 2881, 1957, 1365, 1176, 907; m/z (ESI^+) 220 ($M+H^+$, 100%), HRMS (ESI^+) found 220.0853, $C_9H_{17}O_3NS$ $(M + H)^+$ requires 220.0856.

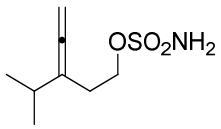
1-Phenylhepta-5,6-dien-3-yl sulfamate (277)



Under an inert atmosphere (nitrogen), formic acid (0.2 mL, 4.0 mmol) was added to neat chlorosulfonyl isocyanate (0.4 mL, 4.0 mmol) at 0 °C with vigorous stirring. After 10 minutes acetonitrile (2 mL) was added and the reaction mixture stirred at room temperature overnight. A solution of 1-phenylhepta-5,6-dien-3-ol **228** (500 mg, 2.7 mmol) in dimethylacetamide (5 mL) was added drop wise and the reaction mixture stirred for 5 hours. The reaction mixture was quenched by the addition of diethyl ether (4 mL) and brine (2 mL). The reaction mixture was poured into diethyl ether (4 mL) and water (3 mL). The separated aqueous phase was further extracted with diethyl ether (3 mL) and the combined organic phase washed with brine (2 x 1.5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (6:1 petroleum ether/

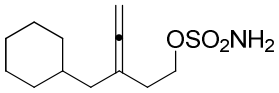
ethyl acetate) afforded the title compound as a yellow oil (421 mg, 1.9 mmol, 71%). δ_H (300 MHz, $CDCl_3$) 7.36 – 7.14 (m, 5H), 5.19 – 5.03 (m, 1H), 4.70 (m, 5H), 2.88 – 2.66 (m, 2H), 2.55 – 2.49 (m, 2H), 2.15 – 2.02 (m, 2H); δ_C (75 MHz, $CDCl_3$) 209.7 (C), 141.0 (C), 128.6 (CH), 128.4 (CH), 126.2 (CH), 84.4 (CH), 83.3 (CH_2), 75.4 (CH), 35.2 (CH_2), 33.4 (CH_2), 31.2 (CH_2); ν_{max}/cm^{-1} 3379, 3281, 2928, 1956, 1355, 1177, 912; m/z (ESI^+) 268 ($M + H^+$, 100%), 204 (45%), 163 (30%); HRMS (ESI^+) found 268.1272, $C_{13}H_{18}O_3NS$ $(M + H)^+$ requires 268.1267.

3-Isopropylpenta-3,4-dien-1-yl sulfamate (278)



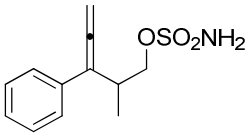
Under an inert atmosphere (nitrogen), formic acid (0.2 mL, 6.0 mmol) was added dropwise to chlorosulfonyl isocyanate (0.5 mL, 6.0 mmol) with vigorous stirring at 0 °C. Acetonitrile (3.6 mL) was added and the reaction mixture warmed to room temperature and stirred overnight. The reaction mixture was cooled to 0 °C, and a solution of 3-isopropylpenta-3,4-dien-1-ol **249** (500 mg, 4.0 mmol) in dimethylacetamide (7.6 mL) was added dropwise and stirred for 30 hours. The reaction was quenched by the addition of ethyl acetate (7 mL) and brine (3.5 mL). The mixture was poured into ethyl acetate (14 mL) and water (5 mL). The separated aqueous phase was further extracted with ethyl acetate (5 mL). The combined organic phase was washed with brine (2 x 5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (1:1 petroleum ether/ethyl acetate) afforded the title compound as a clear oil (581 mg, 2.8 mmol, 54%). δ_H (300 MHz, $CDCl_3$) 4.91 – 4.75 (m, 2H), 4.71 (s, 2H), 4.30 (t, J = 7.2 Hz, 2H), 2.45 – 2.39 (m, 2H), 2.24 – 2.04 (m, 1H), 1.04 (d, J = 6.8 Hz, 6H); δ_C (75 MHz, $CDCl_3$) 204.3 (C), 104.9 (C), 78.3 (CH_2), 69.8 (CH_2), 30.7 (CH), 29.1 (CH_2), 21.3 (CH_3); ν_{max}/cm^{-1} 3378, 3283, 2964, 2932, 2872, 1361, 1176, 971, 918.6; m/z (ESI^+) 223 ($M + H^+$, 100%), 142 (35%); HRMS (ESI^+) found 206.0840, $C_8H_{16}O_3NS$ $(M + H)^+$ requires 206.0845.

3-(Cyclohexylmethyl)penta-3,4-dien-1-yl sulfamate (279)



Under an inert atmosphere (nitrogen), formic acid (0.3 mL, 8.3 mmol) was added drop wise to neat chlorosulfonyl isocyanate (0.7 mL, 8.3 mmol) with vigorous stirring at 0 °C. Acetonitrile (4.5 mL) was added and stirred overnight at room temperature. A solution of 3-(cyclohexylmethyl)penta-3,4-dien-1-ol **252** (1.0 g, 5.6 mmol) in dimethylacetamide (2.5 mL) was added drop wise at 0 °C and stirred for 20 hours. The reaction mixture was quenched by the addition of ethyl acetate (7 mL) and brine (3.5 mL). The mixture was poured into ethyl acetate (14 mL) and water (5 mL). The separated aqueous phase was further extracted with ethyl acetate (10 mL) and the combined organic phase washed with brine (2 x 5 mL) and dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (3:1 petroleum ether/ethyl acetate) afforded the desired material as a clear oil (1.1 g, 4.2 mmol, 76%). δ_H (300 MHz, $CDCl_3$) 4.79 – 4.50 (m, 4H), 4.29 (t, J = 7.1 Hz, 2H), 2.36 (tt, J = 7.0, 3.4 Hz, 2H), 1.91 – 1.82 (m, 2H), 1.82 – 1.57 (m, 4H), 1.51 – 1.32 (m, 1H), 1.31 – 0.99 (m, 4H), 0.99 – 0.73 (m, 2H); δ_C (75 MHz, $CDCl_3$) 206.0 (C), 96.9 (C), 76.4 (CH_2), 69.5 (CH_2), 40.5 (CH_2), 35.8 (CH), 33.3 (CH_2), 31.0 (CH_2), 26.5 (CH_2), 26.2 (CH_2); ν_{max}/cm^{-1} 3274, 2921, 2851, 1959, 1709, 1561, 1448, 1363, 1176. This compound decomposed rapidly; good MS/HRMS data could not be obtained.

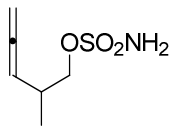
2-Methyl-3-phenylpenta-3,4-dien-1-yl sulfamate (280)



Under an inert atmosphere (nitrogen), formic acid (0.2 mL, 6.0 mmol) was added dropwise to neat chlorosulfonyl isocyanate (0.5 mL, 6.0 mmol) with vigorous stirring at 0

°C. Acetonitrile (3.6 mL) was added and the reaction mixture allowed to warm to room temperature and stirred overnight. The reaction mixture was cooled to 0 °C and 2-methyl-3-phenylpenta-3,4-dien-1-ol **258** (686 mg, 4.0 mmol) in dimethylacetamide (7.6 mL) was added and the reaction mixture stirred for 36 hours. The reaction was quenched by the addition of ethyl acetate (7 mL) and brine (3.5 mL). The reaction mixture was poured into a mixture of ethyl acetate (14 mL) and water (5 mL). The separated aqueous phase was further extracted with ethyl acetate (5 mL). The combined organic phase was washed with brine (2 x 5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (4:1 petroleum ether/ethyl acetate to 2:1 petroleum ether/ethyl acetate) afforded the title compound as a white solid (655 mg, 2.6 mmol, 65%). δ_H (300 MHz, $CDCl_3$) 7.44 – 7.16 (m, 5H), 5.27 – 5.11 (m, 2H), 4.62 (s, 2H), 4.34 (dd, *J* = 9.6, 5.3 Hz, 1H), 4.06 (dd, *J* = 9.5, 8.1 Hz, 1H), 3.23 – 3.01 (m, 1H), 1.27 (d, *J* = 6.8 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 207.9 (C), 135.1 (C), 128.7 (CH), 127.2 (CH), 126.3 (CH), 106.7 (C), 80.4 (CH_2), 74.5 (CH_2), 32.6 (CH), 17.0 (CH_3); ν_{max}/cm^{-1} 3416, 3310, 2982, 2970, 1933, 1542, 1464, 1330, 1170; m/z (ESI^+) 271 ($M + NH_4^+$, 100%), 157 (60%); HRMS (ESI^+) found 271.1115, $C_{12}H_{19}O_3N_2S$ $(M + NH_4)^+$ requires 271.1111.

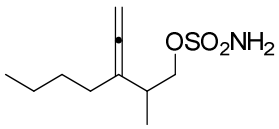
2-Methylpenta-3,4-dien-1-yl sulfamate (281)



Formic acid (0.3 mL, 7.7 mmol) was added dropwise to chlorosulfonyl isocyanate (0.7 mL, 7.7 mmol) at 0 °C with rapid stirring. Acetonitrile (4.6 mL) was added and the mixture stirred overnight. A solution of 2-methylpenta-3,4-dien-1-ol **260** (500 mg, 5.1 mmol) in dimethylacetamide (10 mL) was added dropwise at 0 °C and the reaction mixture stirred overnight. The reaction was quenched by the addition of ethyl acetate (10 mL) and brine (5 mL). The mixture was poured into ethyl acetate (20 mL) and water (7.5 mL). The separated aqueous phase was further extracted with ethyl acetate (7mL). The combined organic layer was washed with brine (2 x 5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (4:1 petroleum

ether/ethyl acetate) afforded the title compound as a clear oil (601 mg, 3.4 mmol, 67%). δ_H (300 MHz, $CDCl_3$) 5.14 (dd, *J* = 13.1, 6.5 Hz, 1H), 4.85 – 4.77 (m, 2H), 4.76 (s, 2H), 4.14 (dd, *J* = 9.4, 6.3 Hz, 1H), 4.04 (dd, *J* = 9.4, 7.0 Hz, 1H), 2.72 – 2.52 (m, 1H), 1.12 (d, *J* = 6.9 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 208.0 (C), 91.2 (CH), 77.2 (CH_2), 75.0 (CH_2), 32.2 (CH), 16.5 (CH_3); ν_{max}/cm^{-1} 3376, 3283, 2974, 1956, 1357, 1175, 972, 919; m/z (ESI^+) 250 (M + OAc^+, 100%), 236 (15%); HRMS (ESI^+) found 178.0529, $C_6H_{11}O_3NS$ (M + H)$^+$ requires 178.0532.

2-Methyl-3-vinylideneheptyl sulfamate (282)



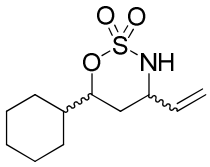
Hept-2-yn-1-ol (2.0 g, 17.9 mmol) was dissolved in triethyl orthopropionate (6.4 mL, 32.0 mmol) and propionic acid (0.2 mL) was added. The flask was fitted with a Dean-Stark apparatus and heated to 150 °C. After stirring for 28 hours propionic acid (0.5 mL) was added and the reaction mixture stirred for a further 10 hours. Purification by column chromatography (16:1 petroleum ether/ethyl acetate) afforded the crude allenoate (2.4 g). The allenoate was dissolved in dry tetrahydrofuran (16 mL) and was added dropwise to a solution of lithium aluminium hydride (846 mg, 22.2 mmol) in dry tetrahydrofuran (8 mL) at 0 °C and warmed to room temperature and stirred for 2 hours. Following a Fieser work up the reaction mixture was filtered through a plug of silica using diethyl ether and concentrated *in vacuo*. Purification by column chromatography (4:1 petroleum ether/ethyl acetate) afforded 2-methyl-3-vinylideneheptan-1-ol **261**[108] as a clear oil (1.3 g, 8.6 mmol, 48% (over 2 steps)). δ_H (300 MHz, $CDCl_3$) 4.81 – 4.71 (m, 2H), 3.69 – 3.49 (m, 2H), 2.34 – 2.00 (m, 1H), 2.00 – 1.89 (m, 2H), 1.56 (br s, 1H), 1.46 – 1.30 (m, 1H), 1.30 – 1.15 (m, 4H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H). This was reacted on below.

Formic acid (0.3 mL, 7.7 mmol) was added dropwise to chlorosulfonyl isocyanate (0.7 mL, 7.7 mmol) at 0 °C with rapid stirring. Acetonitrile (4.6 mL) was added and the

mixture stirred overnight. A solution of 2-methyl-3-vinylideneheptan-1-ol **261** (785 mg, 5.1 mmol) in dimethylacetamide (10 mL) was added dropwise at 0 °C and the reaction mixture stirred overnight. The reaction was quenched by the addition of ethyl acetate (10 mL) and brine (5 mL). The mixture was poured into ethyl acetate (20 mL) and water (7.5 mL). The separated aqueous phase was further extracted with ethyl acetate (7mL). The combined organic layer was washed with brine (2 x 5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (8:1 petroleum ether/ethyl acetate to 4:1 petroleum ether/ethyl acetate) afforded the title compound as a clear oil (925 mg, 4.0 mmol, 78%). δ_H (300 MHz, $CDCl_3$) 4.84 – 4.60 (m, 3H), 4.23 (dd, *J* = 9.4, 5.7 Hz, 1H), 3.98 (dd, *J* = 9.4, 8.0 Hz, 1H), 2.50 – 2.27 (m, 1H), 2.11 – 1.90 (m, *J* = 11.6, 3.4 Hz, 2H), 1.50 – 1.15 (m, 5H), 1.13 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 205.1 (C), 104.3 (C), 78.0 (CH_2), 74.5 (CH_2), 35.3 (CH), 30.5 (CH_2), 29.7 (CH_2), 22.4 (CH_2), 16.5 (CH_3), 13.9 (CH_3); ν_{max}/cm^{-1} 3286, 2958, 2931, 2874, 1954, 1363, 1181, 908; m/z (ESI^+) 273 ($M + NH_4^+$, 100%), 241 (15%), 154 (15%), 137 (70%); HRMS (ESI^+) found 251.1423, $C_{10}H_{23}O_3N_2S$ $(M + NH_4)^+$ requires 251.1424.

6.1.3 Experimental for Chapter 4

6-Cyclohexyl-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide (217)



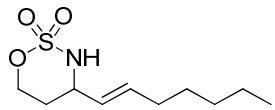
Under an inert atmosphere (nitrogen), 1-cyclohexylpenta-3,4-dien-1-yl sulfamate **216** (60 mg, 0.24 mmol) was dissolved in dry dichloromethane (0.7 mL) and PPh_3AuNTf_2 (8.0 mg, 10.2 µmol) was added. The reaction mixture was stirred for 5 days, then filtered through a plug of silica with diethyl ether and concentrated *in vacuo*. Purification by column chromatography (2:1 hexane/dichloromethane to 1:2 hexane/dichloromethane) afforded the title compound as separable diastereoisomers (60 mg, 0.24 mmol, 99%, *cis*/*trans* = 1.2:1).

cis-**217**: white solid (33 mg, 0.13 mmol); R_f 0.31 (2:1 dichloromethane/hexane); m.p. 91 °C; δ_H (400 MHz, $CDCl_3$) 5.81 (ddd, *J* = 17.3, 10.6, 5.1 Hz, 1H), 5.38 - 5.18 (m, 2H), 4.56 (ddd, *J* = 11.9, 6.4, 2.0 Hz, 1H), 4.31 - 4.17 (m, 1H), 3.98 (d, *J* = 10.3 Hz, 1H), 1.98 - 1.43 (m, 8H), 1.36 - 0.96 (m, 5H); δ_C (101 MHz, $CDCl_3$) 135.3 (CH), 117.3 (CH_2), 88.3 (CH), 56.4 (CH), 42.2 (CH), 32.5 (CH_2), 28.3 (CH_2), 28.0 (CH_2), 26.3 (CH_2), 25.9 (CH_2), 25.7 (CH_2); ν_{max}/cm^{-1} 3276, 2927, 2852, 1650, 1436, 1347, 1175; m/z (ESI^+) 263 (M + NH_4^+, 100%), 246 (15%); HRMS (ESI^+) found 263.1428, $C_{11}H_{23}O_3N_2S$ (M + NH_4)$^+$ requires 263.1424.

trans-**217**: colourless oil (27 mg, 0.11 mmol); R_f 0.15 (2:1 dichloromethane/hexane) δ_H (400 MHz, $CDCl_3$) 6.18 (ddd, *J* = 17.4, 10.7, 5.5 Hz, 1H), 5.28 (ddd, J = 10.7, 1.9, 0.7 Hz, 1H), 5.25 (ddd, *J* = 17.4, 1.8, 0.7 Hz, 1H), 4.67 – 4.56 (m, 1H), 4.48 (d, *J* = 6.6 Hz, 1H), 4.29 - 4.13 (m, 1H), 2.08 – 1.91 (m, 1H), 1.99 - 1.92 (m, 1H), 1.88 (ddd, *J* = 14.5, 3.9, 2.9 Hz, 1H), 1.83 - 1.61 (m, 5H), 1.34 - 0.96 (m, 5H); δ_C (101 MHz, $CDCl_3$) 136.0 (CH),

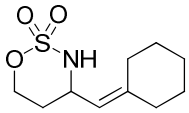
117.2 (CH_2), 86.3 (CH), 55.3 (CH), 41.7 (CH), 30.4 (CH_2), 28.4 (CH_2), 28.2 (CH_2), 26.3 (CH_2), 25.8 (CH_2), 25.6 (CH_2); ν_{max}/cm^{-1} 3277, 2927, 2854, 1645, 1408, 1361, 1175, 870; m/z (ESI^+) 263 (M + NH_4^+, 100%), 246 (15%), 149 (15%); HRMS (ESI^+) found 263.1428, $C_{11}H_{23}O_3N_2S$ $(M + NH_4)^+$ requires 263.1424.

(*E*)-4-(hept-1-en-1-yl)-1,2,3-oxathiazinane 2,2-dioxide (292)



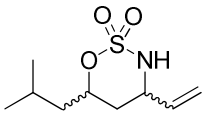
Under an inert atmosphere (nitrogen), deca-3,4-dien-1-yl sulfamate **263** (45 mg, 0.19 mmol) was dissolved in dry dichloromethane (0.7 mL) and PPh_3AuNTf_2 **287** (8.3 mg, 10.6 µmol) was added. The reaction mixture was stirred for 24h, then filtered through a plug of silica with diethyl ether and concentrated *in vacuo*, affording the title compound as a colourless oil (42 mg, 0.18 mmol, 94%). R_f 0.49 (7:3 petroleum ether/ethyl acetate); δ_H (300 MHz, $CDCl_3$) 5.81 - 5.68 (m, 1H), 5.44 - 5.33 (m, 1H), 4.73 (td, *J* = 11.9, 3.1 Hz, 1H), 4.58 - 4.48 (m, 1H), 4.32 - 4.16 (m, 2H), 2.09 - 1.96 (m, 2H), 1.95 - 1.72 (m, 2H), 1.42 - 1.16 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H); δ_C (75.5 MHz, $CDCl_3$) 134.9 (CH), 126.8 (CH), 71.8 (CH_2), 56.9 (CH), 32.3 (CH_2), 31.4 (CH_2), 29.9 (CH_2), 28.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3); ν_{max}/cm^{-1} 3245, 2926, 1433, 1346, 1190, 1170; m/z (ESI^+) 251 (M + NH_4^+, 100%), 216 (6%), 156 (6%); HRMS (ESI^+) found 251.1428, $C_{10}H_{23}O_3N_2S$ $(M + NH_4)^+$ requires 251.1424.

4-(Cyclohexylidenemethyl)-1,2,3-oxathiazinane 2,2-dioxide (293)



Under an inert atmosphere (nitrogen), 4-cyclohexylidenebut-3-en-1-yl sulfamate **267** (50 mg, 0.22 mmol) was dissolved in dry dichloromethane (0.7 mL). PPh_3AuCl (5.4 mg, 10.8 µmol) and AgOTf (2.8 mg, 10.8 µmol) were added. The reaction mixture was stirred for 24 h, then filtered through a plug of silica using diethyl ether as eluent and concentrated *in vacuo*, affording the title compound as a colourless oil (33 mg, 0.14 mmol, 66%). R_f 0.51 (1:1 petroleum ether/ethyl acetate); δ_H (400 MHz, $CDCl_3$) 5.56 - 5.42 (m, 1H), 4.78 - 4.66 (m, 1H), 4.59 - 4.49 (m, 1H), 4.05 - 3.71 (m, 2H), 2.17 (d, *J* = 6.7 Hz, 2H), 2.06 - 1.50 (m, 9H); δ_C (101 MHz, $CDCl_3$) 132.1 (C), 126.5 (CH), 72.2 (CH_2), 53.8 (CH), 44.2 (CH_2), 30.2 (CH_2), 28.5 (CH_2), 25.4 (CH_2), 22.8 (CH_2), 22.2 (CH_2); ν_{max}/cm^{-1} 3246, 2922, 1421, 1347, 1187; m/z (ESI^+) 440 ($M + NH_4^+$, 100%), 232 (43%), 199 (20%), 149 (27%); HRMS (ESI^+) found 249.1271, $C_{10}H_{21}O_3N_2S$ $(M + NH_4)^+$ requires 249.1267.

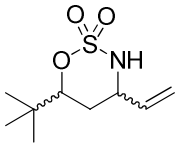
6-Isobutyl-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide (294)



Under an inert atmosphere (nitrogen), 2-methylocta-6,7-dien-4-yl sulfamate **275** (52 mg, 0.24 mmol) was dissolved in dry dichloroethane (0.7 mL) and PPh_3AuNTf_2 **287** (10.0 mg, 12.7 µmol) was added. The reaction mixture was stirred at 40 °C for 5 days, then filtered through a plug of silica with diethyl ether and concentrated *in vacuo*. Purification by column chromatography (4:1 petroleum ether/ethyl acetate) afforded the title compound as an inseparable mixture of diastereoisomers, colourless oil (49 mg, 0.18 mmol, 95%, *cis*/*trans* 1.8:1). R_f 0.52 (4:1 petroleum ether/ethyl acetate); δ_H (300 MHz, $CDCl_3$) *cis*-isomer: 5.81 (ddd, *J* = 17.3, 10.6, 5.0 Hz, 1H), 5.37 - 5.22 (m, 2H), 4.90 - 4.79 (m, 2H), 3.90 (d, *J* = 10.2 Hz, 1H), 1.96 - 1.80 (m, 2H), 1.80-1.66 (m, 1H), 1.60 - 1.45 (2H), 1.00 - 0.87 (m, 6H) *trans*-isomer: 6.18 (ddd, *J* = 17.3, 10.7, 5.5 Hz, 1H), 5.37 - 5.22 (m, 2H), 5.00 - 4.91 (m, 2H), 4.44 (d, *J* = 7.1 Hz, 1H), 1.96 - 1.80 (m, 2H), 1.80 - 1.66 (m, 1H), 1.44 - 1.32 (m, 2H), 1.00 - 0.87 (m, 6H); δ_C (75 MHz, $CDCl_3$) *cis*-isomer: 135.1 (CH), 117.4 (CH_2), 82.7 (CH), 56.3 (CH), 44.3 (CH_2), 35.6 (CH), 23.8 (CH_2), 23.0 (CH_3), 22.0 (CH_3) *trans*-isomer: 135.9 (CH), 117.4 (CH_2), 81.1 (CH), 55.2 (CH), 43.6 (CH_2), 33.5 (CH), 24.1 (CH_2), 23.0 (CH_3), 21.9 (CH_3); ν_{max}/cm^{-1} 3245, 2960, 2874, 1650, 1413, 1356,

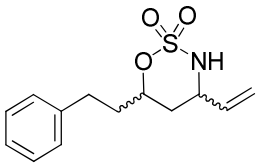
1185; m/z (ESI^+) 237 ($M+NH_4^+$, 100%), HRMS (ESI^+) found 237.1270, $C_9H_{21}O_3N_2S$ $(M + NH_4)^+$ requires 237.1267.

6-(*tert*-Butyl)-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide (295)



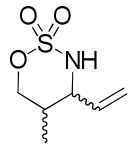
Under an inert atmosphere (nitrogen), 2,2-dimethylhepta-5,6-dien-3-yl sulfamate **276** (57 mg, 0.24 mmol) was dissolved in dry dichloroethane (0.7 mL) and PPh_3AuNTf_2 **287** (10.0 mg, 12.7 µmol) was added. The reaction mixture was stirred at 40 ^oC for 4 days, then filtered through a plug of silica with diethyl ether and concentrated *in vacuo.* Purification by column chromatography (petroleum ether to 2:1 petroleum ether/ethyl acetate) afforded the title compound as an inseparable mixture of diastereoisomers, colourless oil (53 mg, 0.22 mmol, 93%, *cis*/*trans* 2:1). R_f 0.44 (4:1 petrol ether/ethyl acetate); δ_H (300 MHz, $CDCl_3$) *cis*-isomer: 5.82 (ddd, *J* = 17.3, 10.6, 5.0 Hz, 1H), 5.42 - 5.15 (m, 2H), 4.58 - 4.39 (m, 1H), 4.28 - 4.15 (m, 2H), 1.95 – 1.82 (m, 1H), 1.65 – 1.46 (1H, m), 0.98 (s, 9H) *trans*-isomer: 6.20 (ddd, *J* = 17.4, 10.7, 5.4 Hz, 1H), 5.42 - 5.15 (m, 2H), 4.58 – 4.39 (m, 1H), 4.30 - 4.01 (m, 2H), 2.10 - 1.97 (m, 1H), 1.95 – 1.82 (m, 1H), 0.98 (s, 9H); δ_C (75 MHz, $CDCl_3$) *cis*-isomer 135.2 (CH), 117.3 (CH_2), 91.3 (CH), 56.3 (CH), 34.5 (CH_2), 29.9 (C), 25.4 (CH_3) *trans*-isomer 135.9 (CH), 117.1 (CH_2), 88.5 (CH), 55.2 (CH), 34.4 (C), 27.8 (CH_2), 25.2 (CH_3); ν_{max}/cm^{-1} 3252, 2962, 2877, 1650, 1413, 1346, 1183; m/z (ESI^+) 237 ($M + NH_4^+$, 100%) HRMS (ESI^+) found 237.1269, $C_9H_{21}O_3N_2S$ $(M + NH_4)^+$ requires 237.1267.

6-Phenethyl-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide (296)



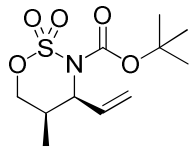
Under an inert atmosphere (nitrogen), 1-phenylhepta-5,6-dien-3-yl sulfamate **277** (50 mg, 0.19 mmol) was dissolved in dry dichloromethane (0.7 mL) and PPh_3AuNTf_2 **287** (7.3 mg, 9.3 μmol) was added. The reaction mixture was stirred at room temperature for 5 days then filtered through a plug of silica with diethyl ether and concentrated *in vacuo*. Purification by column chromatography (6:1 pentane/ethyl acetate to 4:1 pentane/ethyl acetate) afforded the title compound as an inseparable mixture of diastereoisomers, colourless oil (48 mg, 0.18 mmol, 95%, *cis*/*trans* 1.8:1). δ_H (400 MHz, $CDCl_3$) *cis*-isomer: 7.42 - 7.19 (m, 5H), 5.85 (ddd, *J* = 17.3, 10.6, 5.0 Hz, 1H), 5.41 - 5.25 (m, 2H), 4.86 - 4.76 (m, 1H), 4.37 - 4.24 (m, 1H), 4.04 (d, *J* = 10.4 Hz, 1H), 3.00 - 2.71 (m, 2H), 2.22 - 2.04 (m, 1H), 2.03 - 1.86 (m, 2H), 1.63 (dt, *J* = 14.3, 11.9 Hz, 1H) *trans*-isomer: 7.42 – 7.19 (m, 5H), 6.16 (ddd, *J* = 17.2, 10.7, 5.5 Hz, 1H), 5.41 - 5.25 (m, 2H), 4.91 (m, 1H), 4.54 (d, *J* = 6.8 Hz, 1H), 4.37 - 4.24 (m, 1H), 3.00 - 2.71 (m, 2H), 2.36 (dtd, *J* = 14.4, 9.2, 5.3 Hz, 1H), 2.03 - 1.86 (m, 3H); δ_C (75 MHz, $CDCl_3$) *cis*-isomer: 140.4 (C), 135.0 (CH), 128.8 (CH), 128.6 (CH), 126.5 (CH), 117.5 (CH_2), 83.1 (CH), 56.3 (CH), 37.1 (CH_2), 35.2 (CH_2), 30.7 (CH_2) *trans*-isomer: 140.5 (C), 135.6 (CH), 128.7 (CH), 128.6 (CH), 126.4 (CH), 117.5 (CH_2), 81.9 (CH), 55.0 (CH), 36.5 (CH_2), 33.1 (CH_2), 31.1 (CH_2); ν_{max}/cm^{-1} 3263, 3028, 2931, 1603, 1497, 1416, 1360, 1183; m/z (ESI^+) 285 (M + NH_4^+, 100%), 214 (60%); HRMS (ESI^+) found 285.1272, $C_{13}H_{21}O_3N_2S$ (M + NH_4)$^+$ requires 285.1267.

5-Methyl-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide (297)



Under an inert atmosphere (nitrogen), 2-methylpenta-3,4-dien-1-yl sulfamate **281** (50 mg, 0.28 mmol) was dissolved in dry dichloromethane (0.7 mL) and PPh_3AuNTf_2 **287** (13 mg, 16.5 µmol) was added. The reaction mixture was stirred for 3 days at room temperature and flushed through a plug of silica with diethyl ether and concentrated *in vacuo*. Purification by column chromatography (dichloromethane to 1% methanol in dichloromethane) afforded the title compound as a colourless oil (36 mg, 0.23 mmol, 75%, major/minor 3:1); δ_H (400 MHz, $CDCl_3$) major-isomer: 5.81 - 5.66 (m, 1H), 5.42 - 5.23 (m, 2H), 4.84 (dd, *J* = 11.1, 2.5 Hz, 1H), 4.58 - 4.42 (m, 2H), 4.33 (dd, *J* = 11.5, 1.9 Hz, 1H), 2.00 - 1.79 (m, 1H), 1.08 (d, *J* = 7.2 Hz, 3H) minor-isomer: 5.81 – 5.66 (m, 1H), 5.42 – 5.23 (m, 2H), 4.42 – 4.35 (m, 2H), 3.87 (dd, *J* = 17.6, 9.8 Hz, 1H), 2.00-1.79 (m, 1H), 0.89 (d, *J* = 6.8 Hz, 3H); δ_C (101 MHz, $CDCl_3$) major-isomer: 133.9 (CH), 117.0 (CH_2), 77.7 (CH_2), 59.8 (CH), 30.8 (CH), 9.7 (CH_3) minor-isomer: 133.7 (CH), 120.1 (CH_2), 76.4 (CH_2), 63.4 (CH), 33.3 (CH), 12.0 (CH_3); ν_{max}/cm^{-1} 3266, 2977, 1647, 1423, 1358, 1185, 919; m/z (ESI^+) 195 ($M + NH_4^+$, 100%), 187 (10%); HRMS (ESI^+) found 195.0794, $C_6H_{15}O_3N_2S$ $(M + NH_4)^+$ requires 195.0798.

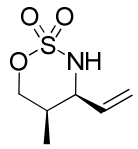
***tert*-Butyl 5-methyl-4-vinyl-1,2,3-oxathiazinane-3-carboxylate 2,2-dioxide (299)**



5-Methyl-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide **297** (188 mg, 1.0 mmol) was dissolved in dry dichloromethane (10 mL) and di-*tert*-butyl dicarbonate (255 mg, 1.2 mmol) was

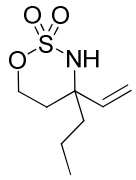
added followed by pyridine (94 µL, 1.2 mmol) and dimethylaminopyridine (13 mg, 0.1 mmol). The reaction mixture was stirred for 18 hours. The reaction mixture was poured into brine (10 mL) and extracted with dichloromethane (3 x 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (1:1 dichloromethane/hexane to dichloromethane) afforded the title compound as a colourless oil (146 mg, 0.5 mmol, 50%). δ_H (300 MHz, $CDCl_3$) 6.02 (ddd, *J* = 17.2, 10.0, 8.4 Hz, 1H), 5.46 – 5.27 (m, 2H), 4.75 (ddd, *J* = 8.4, 4.5, 0.6 Hz, 1H), 4.55 (ddd, *J* = 10.9, 6.5, 0.9, 1H), 4.30 – 4.16 (m, 1H), 2.95 – 2.73 (m, 1H), 1.53 (s, 9H), 0.98 (d, *J* = 7.0 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 150.4 (C), 130.0 (CH), 121.5 (CH_2), 85.2 (C), 74.5 (CH_2), 64.7 (CH), 31.5 (CH), 28.0 (CH_3), 13.4 (CH_3); ν_{max}/cm^{-1} 3266, 2976, 1647, 1424, 1360, 1187, 920; m/z (ESI^+) 295 ($M + NH_4^+$, 100%), 222 (30%); HRMS (ESI^+) found 295.1326, $C_{11}H_{23}O_5N_2S$ $(M + NH_4)^+$ requires 295.1322.

(4*S*,5*R*)-5-methyl-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide (300)



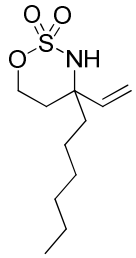
tert-Butyl 5-methyl-4-vinyl-1,2,3-oxathiazinane-3-carboxylate 2,2-dioxide **299** (100 mg, 0.4 mmol) was dissolved in acetonitrile (4 mL) and water (3 mL) and was stirred at 75 °C for 24 hours. After cooling to room temperature aqueous hydrochloric acid (1M; 2 mL) and ethyl acetate (2 mL) were added and the reaction mixture stirred for 1 hour, then basified with aqueous sodium hydroxide (1M). The biphasic mixture was extracted with ethyl acetate (3 times). The combined organic layer washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* affording the title compound as a yellow oil (46mg, 0.26 mmol, 72%). δ_H (300 MHz, $CDCl_3$) 5.76 (ddd, *J* = 17.2, 10.8, 4.3 Hz, 1H), 5.30 (ddd, *J* = 15.6, 10.1, 1.9 Hz, 2H), 4.86 (dd, *J* = 11.5, 2.5 Hz, 1H), 4.64 – 4.45 (m, 1H), 4.33 (dd, *J* = 11.5, 1.8 Hz, 1H), 4.28 – 4.19 (m, 1H), 2.03 – 1.79 (m, 1H), 1.09 (d, *J* = 7.2 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 133.8 (CH), 116.9 (CH_2), 77.6 (CH_2), 59.7 (CH), 30.7 (CH), 9.5 (CH_3); Other data as above. (see Appendix B for crystallographic data)

4-Propyl-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide (302)



Under an inert atmosphere (nitrogen), 3-vinylidenehexyl sulfamate **264** (54 mg, 0.26 mmol) was dissolved in dry dichloromethane (0.7 mL) and PPh_3AuNTf_2 **287** (10.0 mg, 11.4 µmol) was added. The reaction mixture was stirred for 18 h, then filtered through a plug of silica with diethyl ether and concentrated *in vacuo* affording the title compound as a colourless oil (50 mg, 0.24 mmol, 92%). R_f 0.41 (dichloromethane); δ_H (400 MHz, $CDCl_3$) 5.97 - 5.85 (m, 1H), 5.30 (d, *J* = 11.1 Hz, 1H), 5.12 (d, *J* = 17.7 Hz, 1H), 4.73 - 4.64 (m, 1H), 4.60 (ddd, *J* = 11.8, 5.6, 4.0 Hz, 1H), 4.28 (s, 1H), 2.04 - 1.96 (m, 1H), 1.91 - 1.81 (m, 1H), 1.81 - 1.71 (m, 1H), 1.56 - 1.35 (m, 2H), 1.34 - 1.20 (m, 1H), 0.91 (t, *J* = 7.2 Hz, 3H); δ_C (101 MHz, $CDCl_3$) 139.9 (CH), 115.1 (CH_2), 69.2 (CH_2), 63.0 (C), 43.2 (CH_2), 32.2 (CH_2), 16.2 (CH_2), 14.2 (CH_3); ν_{max}/cm^{-1} 3263, 2963, 2876, 1641, 1407, 1354; m/z (ESI^+) 223 ($M + NH_4^+$, 100%), 185 (5%); HRMS (ESI^+) found 223.1113, $C_8H_{19}O_3N_2S$ $(M + NH_4)^+$ requires 223.1111.

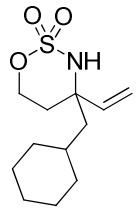
4-Hexyl-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide (303)



Under an inert atmosphere (nitrogen), 3-vinylidenenonyl sulfamate **265** (50 mg, 0.2 mmol) was dissolved in dry dichloromethane (0.7 mL) and PPh_3AuNTf_2 **287** (7.8 mg, 10.0 µmol) was added. The reaction mixture was stirred at room temperature for 48

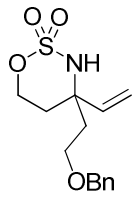
hours. The reaction mixture was filtered through a plug of silica with diethyl ether and concentrated *in vacuo*. Purification by column chromatography (gradient elution: 1:1 petrol ether/dichloromethane to dichloromethane) gave the desired material as a yellow oil (35 mg, 0.14 mmol, 68%). δ_H (300 MHz, $CDCl_3$) 5.91 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.30 (d, *J* = 11.1 Hz, 1H), 5.12 (d, *J* = 17.7 Hz, 1H), 4.77 - 4.48 (m, 2H), 4.16 (s, 1H), 2.01 (m, 1H), 1.92 - 1.70 (m, 2H), 1.60 - 1.51 (m, 1H), 1.44 - 1.14 (m, 8H), 0.88 (dd, *J* = 9.3, 4.2 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 140.0 (CH), 115.2 (CH_2), 69.2 (CH_2), 63.0 (C), 41.1 (CH_2), 32.3 (CH_2), 31.7 (CH_2), 29.4 (CH_2), 22.8 (CH_2), 22.7 (CH_2), 14.2 (CH_3); ν_{max}/cm^{-1} 3264, 2956, 2931, 2859, 1642, 1407, 1356, 1186, 777; m/z (ESI^+) 270 (M + Na^+, 100%); HRMS (ESI^+) found 270.1138, $C_{11}H_{21}O_3NNaS$ $(M + Na)^+$ requires 270.1134.

4-(Cyclohexylmethyl)-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide (304)



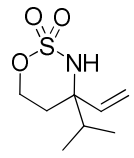
Under an inert atmosphere (nitrogen), 3-(cyclohexylmethyl)penta-3,4-dien-1-yl sulfamate **279** (100 mg, 0.38 mmol) was dissolved in dry dichloroethane (1.4 mL) and PPh_3AuNTf_2 **287** (17.2 mg, 22 µmol) was added. The reaction mixture was stirred at 40 °C for 4 days. The room temperature reaction mixture was filtered through a plug of silica with diethyl ether and concentrated *in vacuo*. Purification by column chromatography (2:1 petroleum ether/diethyl ether) gave the desired material as a colourless oil (37 mg, 0.14 mmol, 37%). δ_H (300 MHz, $CDCl_3$) 6.00 (dd, *J* = 17.8, 11.1 Hz, 1H), 5.31 (d, *J* = 11.1 Hz, 1H), 5.15 (d, *J* = 17.8 Hz, 1H), 4.77 – 4.64 (ddd, *J* = 11.8, 9.4, 3.2, 1H), 4.56 (ddd, *J* = 11.8, 5.0, 4.1 Hz, 1H), 4.12 (s, 1H), 2.06 – 1.83 (m, 2H), 1.72 – 1.37 (m, 6H), 1.31 – 1.04 (m, 4H), 1.04 – 0.82 (m, 3H); δ_C (101 MHz, $CDCl_3$) 140.2 (CH), 115.0 (CH_2), 69.1 (CH_2), 63.4 (C), 49.4 (CH_2), 35.3 (CH_2), 35.0 (CH_2), 33.3 (CH_2), 33.0 (CH), 26.4 (CH_2), 26.4 (CH_2), 26.1 (CH_2); ν_{max}/cm^{-1} 3381, 2921, 2850, 1557, 1449, 1348, 1176, 926; m/z (ESI^+) 282 (M + Na^+, 100%), 278 (40%), 163 (30%); HRMS (ESI^+) found 260.1319, $C_{12}H_{22}O_3NS$ $(M + H)^+$ requires 260.1315.

4-(2-Benzyloxy)ethyl)-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide (305)



Under an inert atmosphere (nitrogen), 3-(2-(Benzyloxy)ethyl)penta-3,4-dien-1-yl sulfamate **266** (50 mg, 0.17 mmol) was dissolved in dry dichloromethane (0.7 mL) and PPh_3AuNTf_2 **287** (6.6 mg, 8.4 µmol) was added. The reaction mixture was stirred at room temperature for 5 days. The room temperature reaction mixture was filtered through a plug of silica with diethyl ether and concentrated *in vacuo*. Purification by column chromatography (9:1 dichloromethane/ ethyl acetate) gave the desired material as a colourless oil (45 mg, 0.15 mmol, 90%). δ_H (300 MHz, $CDCl_3$) 7.47 – 7.26 (m, 5H), 6.00 (ddd, *J* = 17.7, 11.0, 0.6 Hz, 1H), 5.78 (s, 1H), 5.34-5.12 (m, 2H), 4.72 (td, J = 11.4, 2.4 Hz, 1H), 4.60-4.41 (m, 3H), 3.73 – 3.53 (m, 2H), 2.15 – 1.94 (m, 2H), 1.89 – 1.74 (m, 2H); δ_C (75 MHz, $CDCl_3$) 140.3 (CH), 137.1 (C), 128.7 (CH), 128.1 (CH), 128.0 (CH), 115.4 (CH_2), 73.5 (C), 68.8 (CH_2), 65.6 (CH_2), 62.4 (CH_2), 40.1 (CH_2), 30.6 (CH_2); ν_{max}/cm^{-1} 3247, 2874, 1703, 1496, 1455, 1407, 1358, 1187, 778; m/z (ESI^+) 315 (M + NH_4^+, 90%), 298 (M + H)$^+$, 100%), 149 (25%); HRMS (ESI^+) found 298.1115, $C_{14}H_{20}O_4NS$ (M + H)$^+$ requires 298.1108.

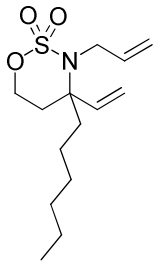
4-Isopropyl-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide (306)



Under an inert atmosphere (nitrogen), 3-isopropylpenta-3,4-dien-1-yl sulfamate **278** (150 mg, 0.7 mmol) was dissolved in dry dichloroethane (2.1 mL) and PPh_3AuNTf_2 **287** (28.7 mg, 36.6 µmol) was added. The reaction mixture was heated to 60 °C and stirred for 24

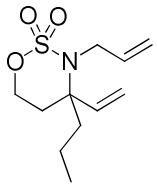
hours. The reaction mixture was filtered through a plug of silica using diethyl ether. Purification by column chromatography (gradient elution: 8:1 petroleum ether/dichloromethane to dichloromethane) afforded the title compound as a white solid (5 mg, 24.4 µmol, 3%). δ_H (400 MHz, $CDCl_3$) 5.87 (ddd, *J* = 17.9, 11.2, 1.0 Hz, 1H), 5.40 (d, *J* = 11.2 Hz, 1H), 5.08 (d, *J* = 17.9 Hz, 1H), 4.71 (ddd, *J* = 11.7, 11.0, 2.6 Hz, 1H), 4.53 (dt, *J* = 11.8, 4.1 Hz, 1H), 4.12 (s, 1H), 2.02 (ddd, *J* = 14.7, 3.8, 2.7 Hz, 1H), 1.97 – 1.76 (m, 2H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 136.3 (CH), 116.7 (CH_2), 69.1 (CH_2), 66.0 (C), 38.1 (CH), 30.2 (CH_2), 16.5 (CH_3), 16.1 (CH_3); ν_{max}/cm^{-1} 3263, 2970, 2881, 1424, 1409, 1359, 1187, 1048, 882, 778.

3-Allyl-4-hexyl-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide (307)



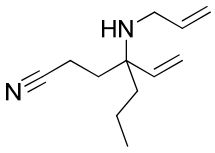
To a solution of 4-hexyl-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide **303** (300 mg, 1.2 mmol) in dichloromethane (8.7 mL) was added benzyltributylammonium bromide (21.4 mg, 60 µmol), allyl bromide (0.4 mL, 4.8 mmol) and sodium hydroxide (5M; 1.7 mL) were added and allowed to stir at room temperature for 24 hours. The separated aqueous layer was further extracted with chloroform (3 x 5 mL). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (9:1 petroleum ether/diethyl ether to 3:2 petroleum ether/diethyl ether) afforded the title compound as a clear oil (299 mg, 1.0 mmol, 87%). δ_H (300 MHz, $CDCl_3$) 5.91 – 5.71 (m, 2H), 5.30 – 5.17 (m, 4H), 4.78 – 4.67 (m, 2H), 4.21 (t, *J* = 7.1 Hz, 2H), 3.83 (d, *J* = 6.4 Hz, 4H), 2.41 – 2.28 (m, 2H), 2.04 – 1.88 (m, 2H), 1.50 – 1.20 (m, 4H), 1.00 – 0.79 (m, 3H); δ_C (100 MHz, $CDCl_3$) 139.4 (CH_2), 135.5 (CH_2), 117.1 (CH), 115.5 (CH), 68.5 (CH_2), 67.4 (C), 48.3 (CH_2), 37.3 (CH_2), 31.8 (CH_2), 31.4 (CH_2), 29.6 (CH_2), 23.8 (CH_2), 22.7 (CH_2), 14.2 (CH_3); ν_{max}/cm^{-1} 3083, 2930, 2858, 1379, 1353, 1175, 922, 787; m/z (ESI^+) 305 ($M + NH_4^+$, 100%), 288 ($M + H^+$, 55%); HRMS (ESI^+) found 288.1624, $C_{14}H_{26}O_3NS$ $(M + H)^+$ requires 288.1628.

3-Allyl-4-propyl-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide (309)



To a stirring solution of 4-propyl-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide **302** (735 mg, 3.6 mmol) in dichloromethane (26 mL) was added benzyltributylammonium bromide (64 mg, 179 µmol), allyl bromide (1.2 mL, 14.3 mmol) and sodium hydroxide solution (5M). The reaction mixture was stirred for 24 hours. Purification by column chromatography (4:1 petroleum ether/ethyl acetate) afforded the title compound as a colourless oil (728 mg, 3.0 mmol, 84%). δ_H (300 MHz, $CDCl_3$) 6.09 (dd, *J* = 17.7, 11.1 Hz, 1H), 5.94 (dddd, *J* = 17.1, 10.2, 6.2, 5.5 Hz, 1H), 5.34 – 5.08 (m, 4H), 4.72 – 4.52 (m, 2H), 3.93 (ddt, *J* = 17.0, 5.4, 1.6 Hz, 1H), 3.74 (ddt, *J* = 17.0, 6.2, 1.4 Hz, 1H), 2.24 – 2.08 (m, 1H), 2.05 – 1.68 (m, 3H), 1.51 – 1.19 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 139.3 (CH), 135.5 (CH), 117.1 (CH_2), 115.5 (CH_2), 68.5 (CH_2), 67.4 (C), 48.3 (CH_2), 39.4 (CH_2), 31.3 (CH_2), 17.2 (CH_2), 14.3 (CH_3); ν_{max}/cm^{-1} 3087, 2964, 2876, 1642, 1379, 1352, 1175; m/z (ESI^+) 263 ($M + NH_4^+$, 70%), 246 ($M + H^+$, 100%); HRMS (ESI^+) found 246.1162, $C_{11}H_{20}O_3NS$ $(M + H)^+$ requires 246.1158.

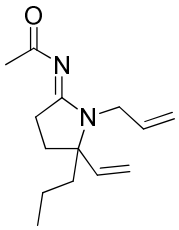
4-(Allylamino)-4-vinylheptanenitrile (310)



3-Allyl-4-propyl-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide **309** (100 mg, 0.41 mmol) was dissolved in dry dimethylformamide (1.4 mL) and potassium cyanide (133 mg, 2.04 mmol) was added and stirred at 40 °C for 2 days. The reaction mixture was diluted with ether (2 mL) and H_2SO_4 (20% aqueous; 2 mL) was added and stirred for 5 hours. The

mixture was neutralised with solid sodium carbonate and extracted with diethyl ether (3 x 5 mL). The combined organic phase was washed with water (x 2), brine and concentrated *in vacuo* to give the desired material as a clear oil (61 mg, 0.3 mmol, 78%). δ_H (300 MHz, $CDCl_3$) 5.90 (ddt, *J* = 17.1, 10.2, 5.8 Hz, 1H), 5.58 (dd, *J* = 17.5, 10.9 Hz, 1H), 5.27-5.01 (m, 4H), 3.02 (dt, *J* = 5.8, 1.5 Hz, 2H), 2.32 (ddd, *J* = 8.3, 6.9, 1.0 Hz, 2H), 1.95-1.63 (m, 2H), 1.54-1.08 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 143.0 (CH), 137.0 (CH), 120.8 (C), 115.5 (CH_2), 114.9 (CH_2), 58.5 (C), 44.3 (CH_2), 39.0 (CH_2), 31.5 (CH_2), 16.4 (CH_2), 14.4 (CH_3), 11.3 (CH_2); ν_{max}/cm^{-1} 3083, 2959, 2933, 2873, 2246, 1643, 1458, 1416, 918; m/z (ESI^+) 193 ($M+H^+$, 100%); HRMS (ESI^+) found 193.1695, $C_{12}H_{21}N_2$ $(M + H)^+$ requires 193.1699.

(*E*)-*N*-(1-Allyl-5-propyl-5-vinylpyrrolidin-2-ylidene)acetamide (314)

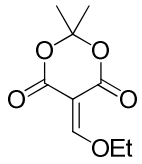


Under an inert atmosphere (nitrogen), diisopropylethylamine (134 mg, 180 µl, 1.04 mmol) was added dropwise to 4-(allylamino)-4-vinylheptanitrile **310** in dry dichloromethane (2.2 mL). The reaction mixture was cooled to 0°C and acetic anhydride (32 mg, 29 µL, 0.31 mmol) was added dropwise followed by dimethylaminopyridine (32 mg, 0.26 mmol). The reaction mixture was heated to reflux for 48 hours. The room temperature reaction mixture was quenched with water (2 mL) followed by H_3PO_4 (5% wt/v; 1 mL) and the organic layer was separated. The aqueous layer was further extracted with dichloromethane (2 x 5 mL) and the combined organic phase was washed with saturated sodium bicarbonate solution and dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (1:1 petroleum ether/ethyl acetate) gave the desired material as a yellow oil (24 mg, 0.1 mmol, 43%). δ_H (400 MHz, $CDCl_3$) 5.90 (dddd, *J* = 17.1, 10.2, 6.9, 5.4 Hz, 1H), 5.78 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.20 – 5.00 (m, 4H), 4.09 (dd, *J* = 15.4, 4.7 Hz, 1H), 3.69 (dd, *J* = 15.3, 6.9 Hz, 1H), 3.13 – 2.94 (m, 1H),

2.94 – 2.76 (m, 1H), 2.14 (s, 3H), 1.95 (t, *J* = 7.9 Hz, 2H), 1.72 (ddd, *J* = 13.7, 12.1, 5.0 Hz, 1H), 1.58 (ddd, *J* = 13.7, 12.0, 4.4 Hz, 1H), 1.43 – 1.05 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 184.3 (C), 170.1 (C), 140.1 (CH), 133.7 (CH), 117.1 (CH_2), 114.7 (CH_2), 69.3 (C), 44.8 (CH_2), 38.9 (CH_2), 31.6 (CH_2), 29.1 (CH_2), 28.0 (CH_3), 17.0 (CH_2), 14.3 (CH_3); ν_{max}/cm^{-1} 2961, 2875, 1642, 1540, 1263, 1249, 990, 925; m/z (ESI^+) 235 ($M + H^+$, 100%), 194 (70%); HRMS (ESI^+) found 235.1806, $C_{14}H_{23}ON_2$ $(M + H)^+$ requires 235.1805.

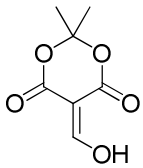
6.1.4 Experimental for Chapter 5

5-(Ethoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (420)[162]



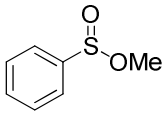
Under an inert atmosphere (nitrogen), triethylorthoformate (28.9 mL, 174 mmol) was added to Meldrum's acid **419** (5.0 g, 35 mmol). The stirring mixture was heated to 100 ^{o}C and stirred for 4 hours. The room temperature reaction mixture was concentrated *in vacuo*, giving the desired product as a yellow-orange unstable solid (3.44 g, 17.2 mmol, 49% crude). δ_H (200 MHz, $CDCl_3$) 8.24 (s, 1H), 4.51 (q, *J* = 7.2 Hz, 2H), 1.73 (s, 6H,), 1.53 (t, *J* = 7.2 Hz, 3H); δ_C (50 MHz, $CDCl_3$) 177.1 (C), 174.0 (C), 160.7 (C), 107.1 (CH), 95.6 (CH_2), 27.3 (CH_3), 15.6 (CH_3). (reacted on as unstable)

5-(Hydroxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (421)[163]



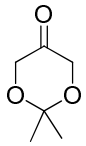
To a stirring solution of 2,2-dimethyl-5-ethoxymethylene-1,3-dioxane-4,6-dione **420** (4.3 g, 22 mmol) in tetrahydrofuran (25 mL) was added hydrochloric acid (2M; 43 mL, 86 mmol) in one portion and the reaction mixture stirred at room temperature for one hour. Saturated sodium chloride (25 mL) was added and the reaction mixture was extracted with diethyl ether (3 x 50 mL). The combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo* giving a yellow solid (3.6 g, 21 mmol, 95%). δ_H (400 MHz, $CDCl_3$) 8.52 (s, 1H), 1.73 (s, 6H) (reacted on as unstable).

Methyl benzenesulfinate (437)[201]



To a solution of diphenyldisulfide **436** (10 g, 46 mmol) in methanol (800 mL) was added sodium carbonate (24.3 g, 229 mmol) followed by bromine (7.0 mL). The reaction mixture was stirred for 3 hours and concentrated *in vacuo*. The reaction mixture was partitioned between dichloromethane (600 mL) and water (400 mL). The layers were separated and the aqueous layer further extracted with dichloromethane (9 x 50 mL). The combined organic phases were combined, dried (Na_2CO_3) and concentrated *in vacuo* giving a yellow oil (13.4 g, 86 mmol, 93%). δ_H (200 MHz, $CDCl_3$) 7.64 - 7.57 (m, 2H), 7.50 - 7.42 (m, 3H), 3.38 (s, 3H); δ_C (50 MHz, $CDCl_3$) 144.1 (C), 132.4 (CH), 129.3 (CH), 125.6 (CH), 49.8 (CH_3); ν_{max}/cm^{-1} 3060, 2942, 1445, 1124.

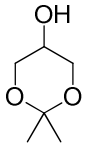
2,2-Dimethyl-1,3-dioxan-5-one (430)[202]



To a cold solution (0 °C) of 5-amino-5-hydroxymethyl-2,2-dimethyl-1,3-dioxane **431** (11.7 g, 73 mmol) and potassium phosphate (9.9 g, 73 mmol) in water (241 mL) was added dropwise *via* an addition funnel a solution of sodium periodate (15.6 g, 73 mmol) in water (211 mL) over 3 hours. The mixture was allowed to stir for an additional hour at 5 °C. The reaction mixture was heated to room temperature and stirred for an additional 17 hours. Sodium thiosulphate (18.0 g, 73 mmol) was added and the resulting solution allowed to stir for 30 minutes. The reaction mixture was extracted with dichloromethane (15 x 50 mL). The combined organic phase was dried (Na_2CO_3), filtered and concentrated *in vacuo* giving a yellow oil (6.0 g, 46 mmol, 63%). δ_H (200 MHz, $CDCl_3$)

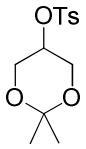
4.03 (s, 4H), 1.34 (s, 6H); δ_C (50 MHz, $CDCl_3$) 208.1 (C=O), 100.1 (C), 66.8 (CH_2), 23.4 (CH_3); ν_{max}/cm^{-1} 2990, 1751, 1374, 1215, 1088.

2,2-Dimethyl-1,3-dioxan-5-ol (439)[203]



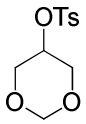
To a solution of 2,2-dimethyl-5-oxo-1,3-dioxane **430** (4.1 g, 31.7 mmol) in dry tetrahydrofuran (100 mL) at 0 °C was added portion wise over 10 minutes, lithium aluminium hydride (1.2 g, 31.7 mmol). The resulting solution was warmed to room temperature and stirred for 1 hour. The reaction mixture was cooled to 0 °C and quenched with water (1.2 mL) then 10% aqueous sodium hydroxide solution (1.2 mL) and finally water (3.5 mL). The reaction mixture was diluted with ethyl acetate (100 mL). The precipitate was filtered off and the separated organic layer dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound as a clear oil (3.7 g, 28 mmol, 89%). δ_H (200 MHz, $CDCl_3$) 4.19 - 3.99 (m, 2H), 3.85 - 3.67 (m, 2H), 3.53 (br s, 1H), 2.85 – 2.74 (m, 1H),1.46 (d, J = 0.5 Hz, 3H), 1.43 (d, J = 0.5 Hz, 3H); δ_C (50 MHz, $CDCl_3$) 97.8 (C), 64.7 (CH_2), 62.9 (CH), 27.3 (CH_3), 18.6 (CH_3); ν_{max}/cm^{-1} 3420, 2993, 2873, 1373, 1197, 1081, 822.

2,2-Dimethyl-1,3-dioxan-5-yl 4-methylbenzenesulfonate (440)[204]



To a solution of 2,2-dimethyl-1,3-dioxan-5-ol **439** (3.4 g, 25.9 mmol) and *p*-toluenesulfonyl chloride (5.4 g, 28.1 mmol) in chloroform (5.5 mL) was added pyridine (2.7 mL) at 0 °C over a period of 10 minutes and then DMAP (2 mg) was added. The reaction mixture was partitioned between chloroform (20 mL) and water (20 mL). The separated aqueous layer was further extracted with chloroform (2 x 10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (5:1 petroleum ether / ethyl acetate) gave the desired material as a white solid (6.4 g, 22.4 mmol, 84%). δ_H (200 MHz, $CDCl_3$) 4.25 - 3.98 (m, 1H), 2.53 (dd, *J* 18.0, 5.7 Hz, 1H), 2.17 (dd, *J* 18.0, 10.0 Hz, 1H), 1.87 - 1.03 (m, 6H), 1.24 (s, 3H), 1.17 (s, 3H), 1.00 - 0.70 (m, 3H); δ_C (50 MHz, $CDCl_3$) 145.2 (C), 133.6 (C), 130.1 (CH), 127.8 (CH), 98.6 (C), 72.1 (CH), 62.1 (CH_2), 61.9 (CH_2), 24.3 (CH_3), 22.5 (CH_3), 21.7 (CH_3); ν_{max} / cm^{-1} 3072, 2983, 1598, 1175.

1,3-Dioxan-5-yl 4-methylbenzenesulfonate (447)[168]



To a solution of glycerol formal **446** (16.6 g, 0.16 mol) and tosyl chloride (31.8 g, 0.17 mol) in chloroform (50 mL) was added pyridine (16 mL) at 0 °C and finally DMAP (5 mg) was added. After stirring for 12 hours the mixture was partitioned between water (20 mL) and chloroform (20 mL). The separated aqueous layer was further extracted with chloroform (2 x 15 mL). The combined organic layer was dried (Na_2SO_4) and

concentrated *in vacuo*. Recrystallisation using ethyl acetate / petroleum ether gave the desired material as a white solid (14.5 g, 55.9 mmol, 58%). δ_H (200 MHz, $CDCl_3$) 7.90 – 7.71 (m, 2H), 7.36 (dd, *J* = 8.1, 0.5 Hz, 2H), 4.86 – 4.68 (m, 2H), 4.55 – 4.36 (m, 1H), 4.09 – 3.65 (m, 4H), 2.45 (s, 3H); δ_C (50 MHz, $CDCl_3$) 145.1 (C), 133.2 (C), 129.8 (CH), 127.6 (CH), 93.2 (CH_2), 70.4 (CH), 68.3 (CH_2), 21.4 (CH_3); ν_{max} / cm^{-1} 3084, 2991, 1586, 1161.

4*H*-1,3-Dioxine (448)[205]

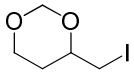
Potassium hydroxide (46.7 g, 0.8 mol) was suspended in triethylene glycol (406 mL) and stirred at 100 °C until a homogeneous solution was obtained. The solution was allowed to cool to 50 °C and 1,3-dioxan-5-yl 4-methylbenzenesulfonate **447** (123 g, 475 mmol) was added in one portion. The solution was heated slowly to 200 °C whilst stirring. The dioxene and water formed were condensed on a cold trap. Purification by distillation followed by drying (Na_2SO_4) gave the desired material as a colourless oil (17.7 g, 0.2 mol, 42%). δ_H (200 MHz, $CDCl_3$) 6.56 (dt, *J* = 6.4, 1.9 Hz, 1H), 5.05 (s, 2H), 4.90 (dt, *J* = 6.4, 2.6 Hz, 2H), 4.24 (dd, *J* = 2.6, 2.0 Hz, 1H); δ_C (50 MHz, $CDCl_3$) 143.1 (CH), 102.4 (CH), 90.0 (CH_2), 63.1 (CH_2). ν_{max}/cm^{-1} 2950, 2862, 2806, 1651, 1476, 1210, 1169, 1120.

3-Iodoprop-1-ene (461)[173]

Allyl bromide **460** (72.6 g, 52 mL, 0.6 mol) and sodium iodide (113 g, 0.8 mol) were dissolved in acetone (200 mL) and heated to 100 °C for 3.5 hours. The reaction mixture was diluted with water (500 mL). The separated organic layer was washed with dilute

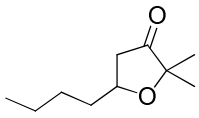
sodium bisulfite solution and then water. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by distillation afforded the title compound as a clear oil (82.0 g, 0.5 mol, 81%). δ_H (200 MHz, $CDCl_3$) 6.22 – 5.90 (m, 1H), 5.24 (d, *J* = 16.8 Hz, 1H), 4.96 (d, *J* = 9.8 Hz, 1H), 3.85 (d, *J* = 7.8 Hz, 2H); δ_C (50 MHz, $CDCl_3$) 135.0 (CH), 117.2 (CH_2), 5.0 (CH_2); ν_{max}/cm^{-1} 3084, 2977, 1721, 1149, 919.

4-(Iodomethyl)-1,3-dioxane (462)[132]



To a suspension of *p*-formaldehyde (23.5 g, 0.8 mol) in dichloromethane (91 mL) at 0 °C was added concentrated H_2SO_4 (15.3 mL) and the mixture stirred at 0°C for 10 minutes. To the resulting solution allyl iodide **461** (74.6 g, 0.4 mol) was added drop wise over 10 minutes and the reaction mixture stirred overnight. The reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with dichloromethane. Purification by distillation gave the desired material as a brown oil (26.0 g, 0.1 mol, 24%). δ_H (200 MHz, $CDCl_3$) 5.07 (d, *J* = 6.3 Hz, 1H), 4.68 (d, *J* = 6.4 Hz, 1H), 4.33 – 3.52 (m, 3H), 3.18 (dd, *J* = 6.0, 1.5 Hz, 2H), 1.89 – 1.63 (m, 2H); δ_C (50 MHz, $CDCl_3$) 94.0 (CH_2), 75.9 (CH), 66.3 (CH_2), 32.0 (CH_2), 7.9 (CH_2); ν_{max}/ cm^{-1} 2853, 1475, 1151.

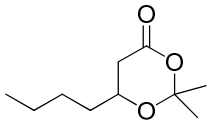
5-Butyl-2,2-dimethyldihydrofuran-3(2H)-one (465)[175]



Under an inert atmosphere (nitrogen), a solution of CuBr.DMS (206 mg, 1 mmol) in dry tetrahydrofuran (10 mL) was cooled to -50 °C, whilst stirring. A solution of butylmagnesium chloride in tetrahydrofuran (1 mL, 2 mmol) was added to the reaction

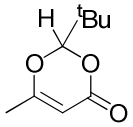
mixture and stirring continued for 30 minutes. The reaction mixture was heated to -30 °C and the stirring continued for a further 30 minutes. The reaction mixture was once again cooled to -50 °C and a solution of 2,2-dimethylfuran-3(2*H*)-one **464** (94 mg, 0.8 mmol) in dry tetrahydrofuran (2 mL) was added. The reaction mixture was poured into saturated ammonium chloride solution (30 mL). The solution was extracted with ethyl acetate (2 x 25 mL) and the combined organic phases were washed with brine and dried ($NaSO_4$) and concentrated *in vacuo*. Purification by column chromatography (3:1 petroleum ether / ethyl acetate) gave the desired material as a clear oil (48 mg, 282 µmol, 34%). δ_H (200 MHz, $CDCl_3$) 4.21 – 4.03 (m, 1H), 2.53 (dd, *J* = 18.0, 5.7, 1H), 2.27 – 2.06 (m, 1H), 1.48 – 1.27 (m, 5H), 1.27 – 1.20 (s, 6H), 1.19 – 1.12 (m, 4H); δ_C (50 MHz, $CDCl_3$) 218.4 (C=O), 80.8 (C), 73.0 (CH), 42.2 (CH_2), 35.9 (CH_2), 27.7 (CH_2), 24.6 (CH_2), 22.9 (CH_3), 21.9 (CH_3), 14.2 (CH_3); ν_{max}/cm^{-1} 2960, 2932, 2863, 1756, 1176, 1112.

6-Butyl-2,2-dimethyl-1,3-dioxan-4-one (467)



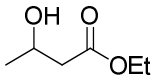
5-Butyl-2,2-dimethyldihydrofuran-3(2*H*)-one **465** (250 mg, 1.5 mmol) and sodium hydrogen carbonate (125 mg, 1.5 mmol) were dissolved in dichloromethane (20 mL). To this stirring solution was added a solution of *meta*-chloroperoxybenzoic acid (256 mg, 1.5 mmol) in dichloromethane (20 mL) and stirred for 2 hours. The reaction mixture was diluted with dichloromethane (20 mL) and washed with 5% sodium hydrogen carbonate solution and brine. Purification by column chromatography afforded the title compound as a clear oil (95 mg, 0.5 mmol, 34%). δ_H (200 MHz, $CDCl_3$) 4.25 – 3.98 (m, 1H), 2.53 (dd, *J* = 18.0, 5.7 Hz, 1H), 2.17 (dd, *J* = 18.0, 10.0 Hz, 1H), 1.87 – 1.73 (m, 6H), 1.24 (s, 3H), 1.17 (s, 3H), 1.00 – 0.70 (m, 3H); ν_{max}/cm^{-1} 2958, 2931, 2863, 1755, 1175, 1112.

2-(*tert*-butyl)-6-methyl-4*H*-1,3-dioxin-4-one (472)[161]



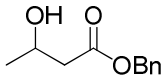
Under an inert atmosphere (nitrogen), in a microwave vial, 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **468** (0.1 g, 0.1 mL, 0.8 mmol) and pivaldehyde (1.6 mL, 1.3 g, 15.1 mmol) were dissolved in ethyl acetate (4 mL) in the presence of molecular sieves (1.5 g). This was stirred in the microwave reactor at 120 °C for 20 minutes. The reaction mixture was concentrated *in vacuo*, and purified by column chromatography affording the title compound (56 mg, 0.3 mmol, 38%). δ_H (200 MHz, $CDCl_3$) 5.26 (s, 1H), 5.01 (s, 3H), 2.01 (s, 9H); δ_C (50 MHz, $CDCl_3$) 172.2 (C=O), 106.1 (CH), 95.9 (CH), 34.4 (C), 31.0 (C), 24.1 (CH_3), 19.4 (CH_3). ν_{max}/cm^{-1} 2967, 2877, 1736, 1630, 1394, 1344, 1218, 1080.

Ethyl 3-hydroxybutanoate (476)[206]



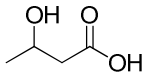
Ethyl acetoacetate **475** (5.0 g, 38.5 mmol) in ethanol (100 mL) was treated with sodium borohydride (719 mg, 19 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound (4.1 g, 31.1 mmol, 82%). δ_H (200MHz, $CDCl_3$) 4.22 - 4.11 (m, 3H), 2.95 (br s, 1H), 2.52 – 2.36 (m, 2H), 1.35 – 1.15 (m, 6H); δ_C (50 MHz, $CDCl_3$) 173.8 (C=O), 64.2 (CH), 61.1 (CH_2), 44.4 (CH_2), 23.4 (CH_3), 14.9 (CH_3); ν_{max}/cm^{-1} 3441, 2978, 2936, 1717, 1401, 1374, 1296, 1179.

Benzyl 3-hydroxybutanoate (478)[207]



Benzyl acetoacetate **477** (20 g, 0.1 mol) was dissolved in dry tetrahydrofuran (1.0 L) and water (200 mL). At 0°C, sodium borohydride (1.1 g, 30 mmol) was added and the reaction mixture stirred for 20 minutes. Sodium borohydride (0.4 g, 10 mmol) was added after a further 15 minutes a final portion of sodium borohydride (0.4 g, 10 mmol) was added. The reaction mixture was stirred for 1 hour and water (500 mL) was added slowly to the reaction mixture. The separated aqueous phase was extracted with diethyl ether (5 x 180 mL) and the combined organic phase dried ($MgSO_4$) and concentrated *in vacuo* affording the title compound as a yellow liquid (19.6 g, 0.1 mol, 97%). δ_H (200MHz, $CDCl_3$) 7.43 – 7.30 (m, 5H), 5.15 (s, 2H), 4.30 – 4.12 (m, 1H), 2.95 (d, *J* = 3.6 Hz, 1H), 2.57 – 2.44 (m, 2H), 1.26 – 1.16 (m, 3H); δ_C (50 MHz, $CDCl_3$) 171.2 (C=O), 145.4 (C), 129.2 (CH), 124.8 (CH), 121.2 (CH), 66.4 (CH_2), 63.7 (CH), 43.7 (CH_2), 22.5 (CH_3); ν_{max}/cm^{-1} 3413, 2976, 2932, 1753, 1398, 1372.

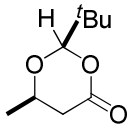
3-Hydroxybutanoic acid (479)[208]



Method 1: Ethyl 3-hydroxybutanoate **476** (500 mg, 3.8 mmol) was added to KOH (10% aqueous solution) at 0°C and stirred for one hour. The solution was acidified (3M HCl) to a pH of 6. The aqueous phase was extracted with a 3:1 mixture of chloroform / isopropyl alcohol. The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*, giving the desired material as a yellow oil (2.2 g, 21.4 mmol, 78%).

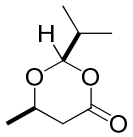
Method 2: Benzyl 3-hydroxybutanoate **478** (16.6 g, 85.3 mmol) was dissolved in ethyl acetate (180 mL) and Pd/C (10%; 5.1 g) was added and the reaction mixture placed under an atmosphere of hydrogen for 67 hours. The resction mixture was filtered through celite and concentrated *in vacuo* to give the desired product as a yellow liquid (5.7 g, 54.8 mmol, 64%). δ_H (200MHz, $CDCl_3$) 7.43 – 7.30 (m, 5H), 5.15 (s, 2H), 4.30 – 4.12 (m, 1H), 2.95 (d, *J* = 3.6 Hz, 1H), 2.57 – 2.44 (m, 2H), 1.26 – 1.16 (m, 3H); δ_C (50 MHz, $CDCl_3$) 177.0 (C=O), 64.1 (CH), 42.3 (CH), 22.1 (CH_3); ν_{max}/cm^{-1} 2978, 1729, 1382, 1300, 1186, 1056.

2-(*tert*-butyl)-6-methyl-1,3-dioxan-4-one (473)[209]



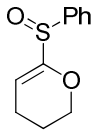
3-Hydroxybutanoic acid **479** (1.0 g, 9.8 mmol) and pivaldehyde (2.5 g, 29.5 mmol) were dissolved in benzene (30 mL). Pyridinium *p*-toluenesulfonate (246 mg, 1.0 mmol) and molecular sieves (4Å sieves; 2.2 g) were added. The reaction mixture was stirred at reflux for 46 hours. The room temperature reaction mixture was filtered and diluted with dichloromethane. Saturated sodium hydrogen carbonate solution was added. The separated aqueous layer was further extracted with dichloromethane (2 x 25 mL). The combined organic phase was washed with saturated sodium hydrogen carbonate solution and dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound (1.5 g, 6.6 mmol, 68%). δ_H (400 MHz, $CDCl_3$) 4.90 (s, 1H), 3.97 (dqd, *J* = 10.5, 6.1, 4.3 Hz, 1H), 2.65 (dd, *J* = 17.7, 4.3 Hz, 1H), 2.36 (dd, *J* = 17.7, 10.7 Hz, 1H), 1.32 (d, *J* = 6.1 Hz, 3H), 0.98 (s, 9H); δ_C (100 MHz, CDCl3) 168.3 (C=O), 108.6 (CH), 70.4 (CH), 37.8 (CH_2), 35.2 (C), 24.0 (CH_3), 21.2 (CH_3); ν_{max}/cm^{-1} 2980.6, 2966, 2919, 2874, 1727, 1482, 1455, 1421.

2-Isopropyl-6-methyl-1,3-dioxan-4-one (480)[209]



3-Hydroxybutanoic acid **479** (1.4 g, 13.3 mmol), isobutyraldehyde (2.9 g, 39.9 mmol) and pyridinium *p*-toluenesulfonate (333 mg, 0.1 mmol) were dissolved in benzene (40 mL) in the presence of molecular sieves (4 Å; 2.8 g). The reaction mixture was refluxed for 16 hours. The room temperature reaction mixture was concentrated *in vacuo*. The residue was dissolved in dichloromethane (50 mL) and washed with saturated sodium hydrogen carbonate solution (3 x 20 mL) and the combined organic phase dried (Na_2SO_4) and concentrated *in vacuo* giving a clear oil (1.7 g, 10.9 mmol, 82%). δ_H (200 MHz, $CDCl_3$) 5.10 (d, *J* = 4.3 Hz, 1H), 4.01 (dqd, *J* = 10.6, 6.1, 4.3 Hz, 1H), 2.68 (dd, *J* = 17.7, 4.3 Hz, 1H), 2.40 (dd, *J* = 17.8, 10.7 Hz, 1H), 2.13 – 1.72 (m, 1H), 1.35 (d, *J* = 6.1 Hz, CH_3), 1.02 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H); δ_C (50 MHz, $CDCl_3$) 168.3 (C=O), 106.6 (CH), 70.4 (CH), 37.6 (CH_2), 32.6 (CH), 21.7 (CH_3), 16.0 (CH_3); ν_{max}/cm^{-1}2981, 2845, 1738, 1382, 1338, 1249.

6-(Phenylsulfonyl)-3,4-dihydro-2*H*-pyran (484)



Flask 1. Preparation of the enol triflate **482**: A solution of KHMDS (1M in tetrahydrofuran) in tetrahydrofuran (6.8 mL) was cooled to -78 °C. A mixture of *N*-phenyl-bis(trifluoromethanesulfonimide) (0.86 g, 2.4 mmol) and δ-valerolactone **481** (0.2 g, 2.0 mmol) in tetrahydrofuran (10 mL) was added over a period of 1 hour. After addition was complete, the reaction mixture was allowed to stir for 15 minutes at -78 °C.

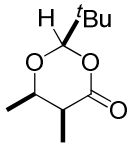
Flask 2. Preparation of sodium benzenethiolate: Benzenethiol (264 mg, 2.4 mmol) was added to a suspension of sodium hydride (60% dispersion in oil; 0.16g, 4.0 mmol) in tetrahydrofuran (2 mL) and stirred for 15 minutes and cooled to -78 °C.

Flask 3. Preparation of the Ni(0) Catalyst: To a solid mixture of $Ni(Ph_3P)_2Br_2$ (149 mg, 0.2 mmol), triphenylphosphine (105 mg, 0.4 mmol) and zinc powder (78 mg, 1.2 mmol) was added tetrahydrofuran (4.6 mL) at room temperature. The green solid suspension was stirred until a dark red solution was formed (about 1 min).

The contents of flask 1 (the enol triflate) were transferred by cannula to flask 2 (the sodium benzenethiolate) at -78 °C whereupon the contents of flask 3 [the Ni(0) catalyst] were added. The cooling bath was removed and the reaction mixture stirred at room temperature for 2 hours. Aqueous 5% sodium hydroxide (50 mL) was added and the reaction mixture was extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on alumina (hexanes containing 0.5% NEt_3) to give a mixture of the sulfide **483** and the triflate starting material **482**. This was reacted on.

The sulfide **483** in dichloromethane (5 mL) and sodium bicarbonate (702 mg, 8.4 mmol) was cooled to -78 °C. *m*-CPBA (385 mg, 2.2 mmol) in dichloromethane (5 mL) was added dropwise over 10 minutes. The reaction mixture was stirred at -78 °C for 3 hours and then warmed to room temperature and stirred for an additional 18 hours. The reaction mixture was quenched with saturated $Na_2S_2O_3$ solution (5 mL). The separated aqueous phase was further extracted with dichloromethane (2 x 10 mL) and the combined organic phase concentrated *in vacuo*. Purification by column chromatography (gradient elution: 4:1 petroleum ether / ethyl acetate to 2:1 petroleum ether to ethyl acetate) giving a clear oil (103 mg, 0.5 mmol, 25% (over 2 steps)). δ_H (400 MHz, $CDCl_3$) δ 7.97 – 7.89 (m, 2H), 7.66 – 7.48 (m, 3H), 6.14 (t, J = 4.0 Hz, 1H), 4.08 – 4.01 (m, 2H), 2.23 (td, J = 6.4, 4.1 Hz, 2H), 1.89 – 1.78 (m, 2H). Attempted purification by column chromatography led to decomposition of material.

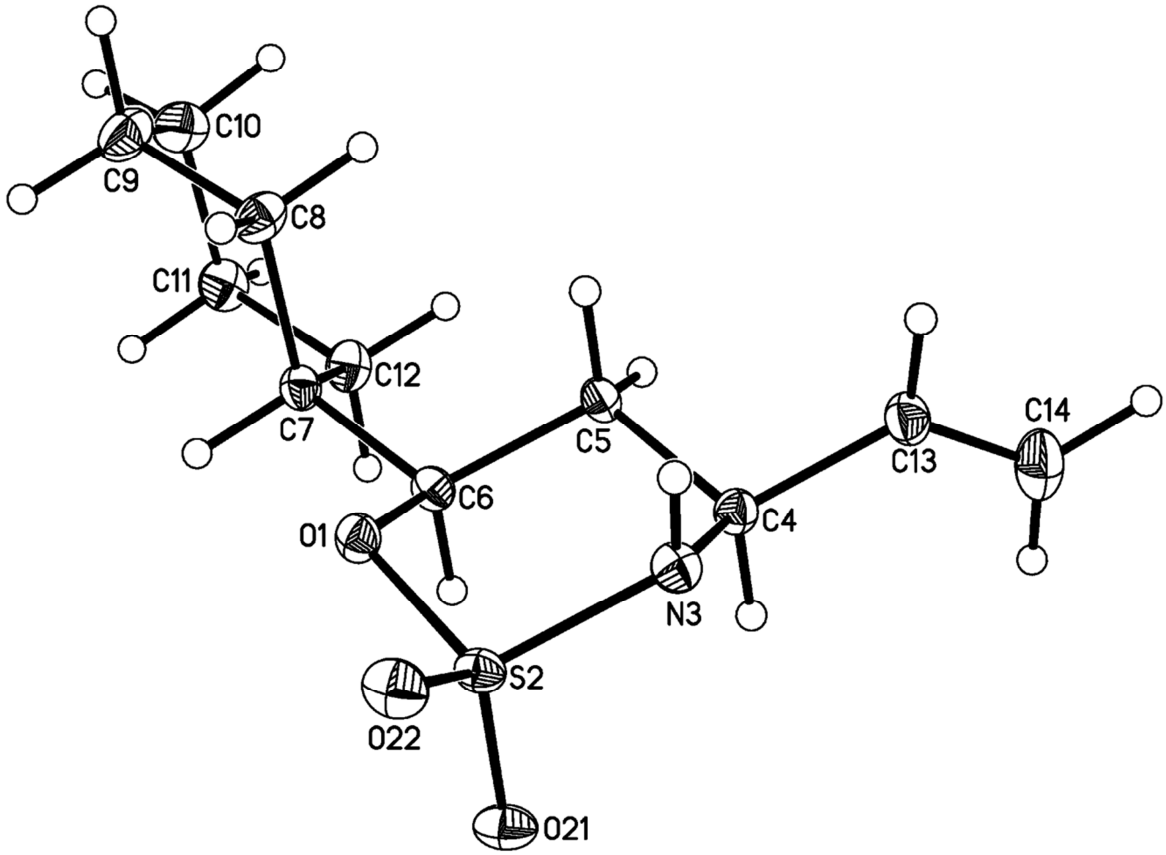
2-(*tert*-butyl)-5,6-dimethyl-1,3-dioxan-4-one (485)[160]



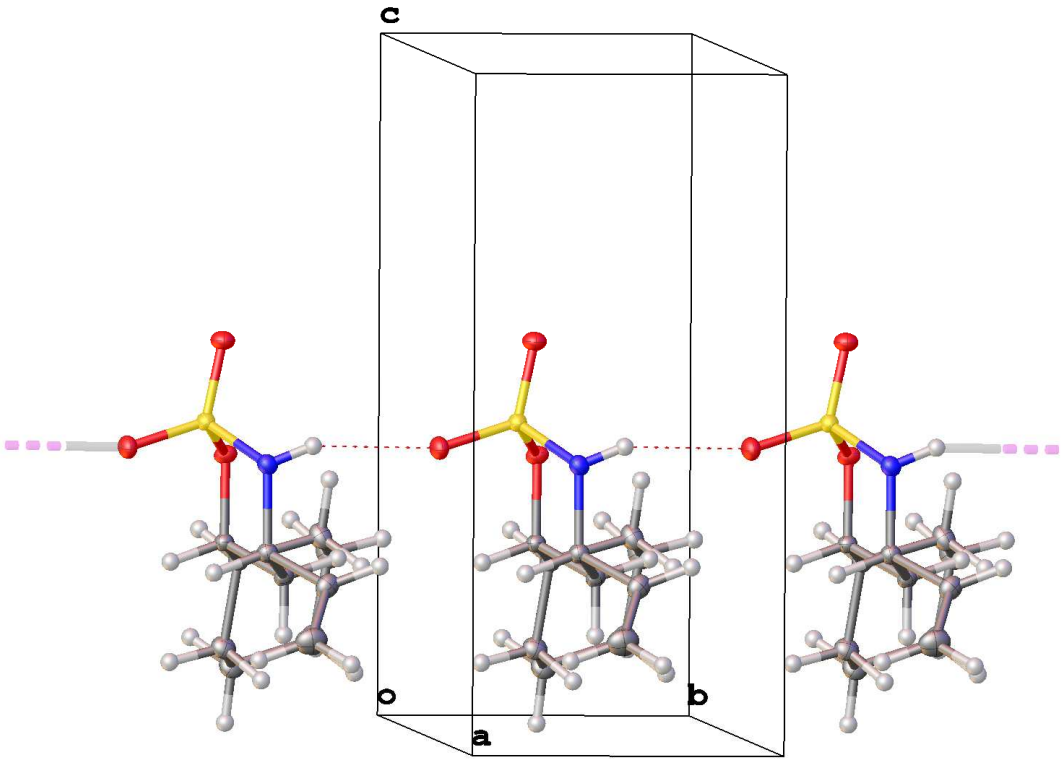
At 0 °C to diisopropylamine (2.3 mL, 1.6 mmol) in tetrahydrofuran (0.25 mL) was added *n*-butyllithium (2.5 M in hexanes; 1.6 mmol). The yellow solution was cooled down to -78 °C and diluted with tetrahydrofuran (2.3 mL). A solution of 2-*tert*-butyl-6-methyl-1,3-dioxan-4-one **473** (250 mg, 1.5 mmol) in tetrahydrofuran (1 mL) was dropped into the solution at -78 °C and the solution stirred for 30 minutes. After the addition of the methyl iodide (0.65 mL, 2.9 mmol) the reaction mixture was allowed to reach room temperature over 16 hours. Buffer solution (pH 7; 5 mL) was added in one portion after warming to room temperature. It was extracted with diethyl ether (3 x 5 mL) and the combined organic phase dried (Na_2SO_4) and concentrated *in vacuo* to give a white solid (167 mg, 0.9 mmol, 62%). δ_H (400 MHz, $CDCl_3$) 4.95 (s, 1H), 3.64 (dq, *J* = 10.5, 6.1 Hz, 1H), 2.36 (dq, *J* = 10.4, 7.3 Hz, 1H), 1.36 (d, *J* = 6.1 Hz, 3H), 1.27 (d, *J* = 7.3 Hz, 3H), 0.98 (s, 9H); δ_C (75 MHz, $CDCl_3$) 171.7 (C=O), 108.2 (CH), 65.7 (CH), 43.0 (CH), 35.2 (C), 23.9 (CH_3), 19.6 (CH_3), 12.4 (CH_3); ν_{max}/cm^{-1} 2979, 1750, 1476, 1458, 1408, 1388.

Appendix A: X-ray data of *cis*-6-cyclohexyl-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide (217)

Structure determination for X83875: Mari Higginbotham MCH260B



Displacement ellipsoids drawn at the 50% probability level.
NH..O Hydrogen bonding



Data collection

A single crystal was coated in Paratone-N heavy oil then placed on a Mitigen MicroMount fixed to the goniometer head which was put in a cold stream of nitrogen gas (100K) on a Bruker Nonius X8 Apex2 CCD diffractometer. Data were integrated using SAINT then scaled with SADABS Structure solution and refinement were performed using the SHELXTL suite of programs.

Program reference:

APEX2 (SAINT, SADABS, SHELXTL) Bruker AXS Inc., Madison, Wisconsin, USA. 2004-2010

Table 1. Crystal data and structure refinement for 3875./ MCH260B

Identification code	3875	
Empirical formula	C11 H19 N O3 S	
Formula weight	245.33	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 19.8419(15) Å	□= 90°.
	b = 5.3049(4) Å	□= 90.646(4)°.
	c = 11.5941(9) Å	□ = 90°.
Volume	1220.31(16) Å^3	

Z	4
Density (calculated)	1.335 Mg/m^3
Absorption coefficient	0.258 mm^{-1}
F(000)	528
Crystal size	0.56 x 0.38 x 0.24 mm^3
Theta range for data collection	3.51 to 32.06°.
Index ranges	-29<=h<=29, -7<=k<=7, -17<=l<=17
Reflections collected	27110
Independent reflections	4215 [R(int) = 0.0325]
Completeness to theta = 25.00°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9406 and 0.8689
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4215 / 0 / 154
Goodness-of-fit on F^2	1.049
Final R indices [I>2sigma(I)]	R1 = 0.0329, wR2 = 0.0846
R indices (all data)	R1 = 0.0417, wR2 = 0.0890
Largest diff. peak and hole	0.662 and -0.366 $e.Å^{-3}$

Table 2. Bond lengths [Å] and angles [°] for 3875.

S(2)-O(22)	1.4238(8)
S(2)-O(21)	1.4379(8)
S(2)-O(1)	1.5792(7)
S(2)-N(3)	1.6254(9)
O(1)-C(6)	1.4946(11)
N(3)-C(4)	1.5011(12)
N(3)-H(3)	0.838(15)
C(4)-C(13)	1.5022(14)
C(4)-C(5)	1.5350(13)
C(4)-H(4)	1.0000
C(5)-C(6)	1.5240(13)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-C(7)	1.5253(13)
C(6)-H(6)	1.0000
C(7)-C(8)	1.5362(14)
C(7)-C(12)	1.5365(14)
C(7)-H(7)	1.0000
C(8)-C(9)	1.5328(15)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.5314(16)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.5317(16)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-C(12)	1.5326(14)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-C(14)	1.3228(15)
C(13)-H(13)	0.9500
C(14)-H(14A)	0.947(17)
C(14)-H(14B)	0.973(16)

O(22)-S(2)-O(21)	119.56(5)

O(22)-S(2)-O(1)	105.57(4)
O(21)-S(2)-O(1)	108.48(4)
O(22)-S(2)-N(3)	109.24(5)
O(21)-S(2)-N(3)	107.80(5)
O(1)-S(2)-N(3)	105.30(4)
C(6)-O(1)-S(2)	114.74(6)
C(4)-N(3)-S(2)	113.10(6)
C(4)-N(3)-H(3)	111.5(9)
S(2)-N(3)-H(3)	110.7(10)
N(3)-C(4)-C(13)	108.67(8)
N(3)-C(4)-C(5)	110.12(7)
C(13)-C(4)-C(5)	111.53(8)
N(3)-C(4)-H(4)	108.8
C(13)-C(4)-H(4)	108.8
C(5)-C(4)-H(4)	108.8
C(6)-C(5)-C(4)	112.17(8)
C(6)-C(5)-H(5A)	109.2
C(4)-C(5)-H(5A)	109.2
C(6)-C(5)-H(5B)	109.2
C(4)-C(5)-H(5B)	109.2
H(5A)-C(5)-H(5B)	107.9
O(1)-C(6)-C(5)	108.82(7)
O(1)-C(6)-C(7)	105.51(7)
C(5)-C(6)-C(7)	115.90(8)
O(1)-C(6)-H(6)	108.8
C(5)-C(6)-H(6)	108.8
C(7)-C(6)-H(6)	108.8
C(6)-C(7)-C(8)	114.13(8)
C(6)-C(7)-C(12)	110.49(8)
C(8)-C(7)-C(12)	110.05(8)
C(6)-C(7)-H(7)	107.3
C(8)-C(7)-H(7)	107.3
C(12)-C(7)-H(7)	107.3
C(9)-C(8)-C(7)	110.61(8)
C(9)-C(8)-H(8A)	109.5
C(7)-C(8)-H(8A)	109.5
C(9)-C(8)-H(8B)	109.5
C(7)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	108.1
C(10)-C(9)-C(8)	111.04(9)

C(10)-C(9)-H(9A)	109.4
C(8)-C(9)-H(9A)	109.4
C(10)-C(9)-H(9B)	109.4
C(8)-C(9)-H(9B)	109.4
H(9A)-C(9)-H(9B)	108.0
C(9)-C(10)-C(11)	110.95(9)
C(9)-C(10)-H(10A)	109.4
C(11)-C(10)-H(10A)	109.4
C(9)-C(10)-H(10B)	109.4
C(11)-C(10)-H(10B)	109.4
H(10A)-C(10)-H(10B)	108.0
C(10)-C(11)-C(12)	111.38(9)
C(10)-C(11)-H(11A)	109.4
C(12)-C(11)-H(11A)	109.4
C(10)-C(11)-H(11B)	109.4
C(12)-C(11)-H(11B)	109.4
H(11A)-C(11)-H(11B)	108.0
C(11)-C(12)-C(7)	111.07(8)
C(11)-C(12)-H(12A)	109.4
C(7)-C(12)-H(12A)	109.4
C(11)-C(12)-H(12B)	109.4
C(7)-C(12)-H(12B)	109.4
H(12A)-C(12)-H(12B)	108.0
C(14)-C(13)-C(4)	123.37(11)
C(14)-C(13)-H(13)	118.3
C(4)-C(13)-H(13)	118.3
C(13)-C(14)-H(14A)	121.1(9)
C(13)-C(14)-H(14B)	122.5(9)
H(14A)-C(14)-H(14B)	116.4(13)

Symmetry transformations used to generate equivalent atoms:

Table 3. Torsion angles [°] for 3875.

O(22)-S(2)-O(1)-C(6)	170.61(6)
O(21)-S(2)-O(1)-C(6)	-60.10(7)
N(3)-S(2)-O(1)-C(6)	55.09(7)
O(22)-S(2)-N(3)-C(4)	-166.05(7)
O(21)-S(2)-N(3)-C(4)	62.59(8)
O(1)-S(2)-N(3)-C(4)	-53.07(7)
S(2)-N(3)-C(4)-C(13)	178.83(7)
S(2)-N(3)-C(4)-C(5)	56.40(9)
N(3)-C(4)-C(5)-C(6)	-58.54(10)
C(13)-C(4)-C(5)-C(6)	-179.27(8)
S(2)-O(1)-C(6)-C(5)	-59.39(9)
S(2)-O(1)-C(6)-C(7)	175.62(6)
C(4)-C(5)-C(6)-O(1)	58.77(10)
C(4)-C(5)-C(6)-C(7)	177.42(8)
O(1)-C(6)-C(7)-C(8)	65.82(10)
C(5)-C(6)-C(7)-C(8)	-54.64(11)
O(1)-C(6)-C(7)-C(12)	-169.54(8)
C(5)-C(6)-C(7)-C(12)	70.00(11)
C(6)-C(7)-C(8)-C(9)	-177.47(9)
C(12)-C(7)-C(8)-C(9)	57.66(11)
C(7)-C(8)-C(9)-C(10)	-57.46(12)
C(8)-C(9)-C(10)-C(11)	55.82(12)
C(9)-C(10)-C(11)-C(12)	-54.98(12)
C(10)-C(11)-C(12)-C(7)	55.83(12)
C(6)-C(7)-C(12)-C(11)	176.18(8)
C(8)-C(7)-C(12)-C(11)	-56.89(11)
N(3)-C(4)-C(13)-C(14)	126.83(11)
C(5)-C(4)-C(13)-C(14)	-111.59(12)

Symmetry transformations used to generate equivalent atoms:

Table 4. Hydrogen bonds for 3875 [Å and °].

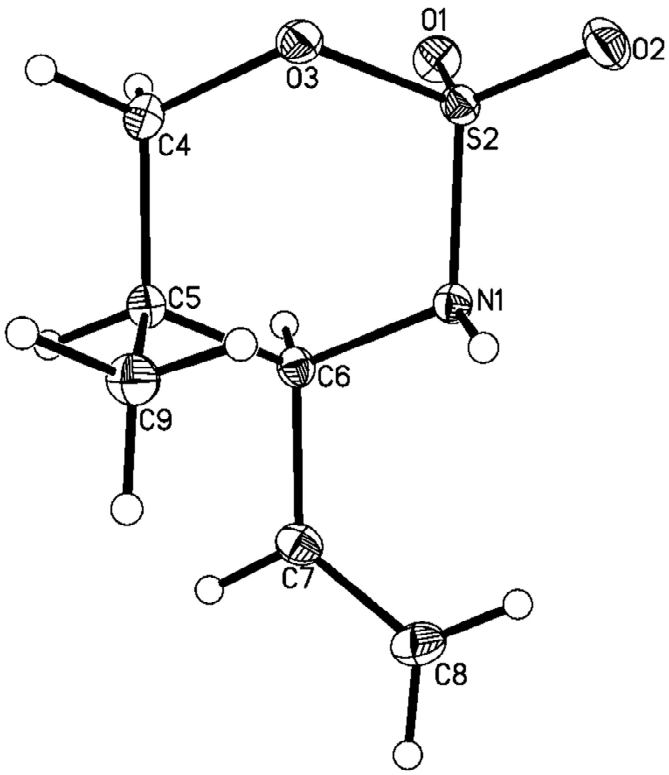
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(3)-H(3)...O(21)#1	0.838(15)	2.356(15)	3.1188(12)	151.7(13)

Symmetry transformations used to generate equivalent atoms:

#1 x,y+1,z

Appendix B: X-ray data for (4*S*,5*R*)-5-methyl-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide (300)

MCH360C crystal structure



Perspective view of MCH360C. Displacement ellipsoids drawn at the 50% probability level

The crystal structure is an inverted twin. Both RS and SR forms exist. The major component in this crystal is shown above.

Table 1. Crystal data and structure refinement for MCH360C/4216.

Identification code	4216
Empirical formula	C6 H11 N O3 S
Formula weight	177.22
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic

Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.7599(5) Å	α= 90°.
	b = 8.3411(6) Å	β= 90°.
	c = 14.1011(11) Å	γ = 90°.
Volume	795.09(10) $Å^3$	
Z	4	
Density (calculated)	1.480 Mg/m^3	
Absorption coefficient	0.365 mm^{-1}	
F(000)	376	
Crystal size	0.56 x 0.40 x 0.34 mm^3	
Theta range for data collection	2.84 to 36.03°.	
Index ranges	-11<=h<=11, -13<=k<=13, -23<=l<=22	
Reflections collected	26398	
Independent reflections	3734 [R(int) = 0.0196]	
Completeness to theta = 25.00°	99.8 %	
Absorption correction	None	
Max. and min. transmission	0.8860 and 0.8218	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3734 / 0 / 102	
Goodness-of-fit on F^2	1.085	
Final R indices [I>2sigma(I)]	R1 = 0.0206, wR2 = 0.0569	
R indices (all data)	R1 = 0.0214, wR2 = 0.0574	
Absolute structure parameter	0.48(3)	
Largest diff. peak and hole	0.394 and -0.294 $e.Å^{-3}$	

Table 2. Bond lengths [Å] and angles [°] for 4216.

N(1)-C(6)	1.4876(7)
N(1)-S(2)	1.6183(6)
N(1)-H(1)	0.886(11)
O(1)-S(2)	1.4356(5)
O(2)-S(2)	1.4239(6)
S(2)-O(3)	1.5810(5)
O(3)-C(4)	1.4790(9)
C(4)-C(5)	1.5257(10)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(9)	1.5311(9)
C(5)-C(6)	1.5469(8)
C(5)-H(5)	1.0000
C(6)-C(7)	1.5024
C(6)-H(6)	1.0000
C(7)-C(8)	1.3265
C(7)-H(7)	0.9500
C(8)-H(8A)	0.9500
C(8)-H(8B)	0.9500
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800

C(6)-N(1)-S(2)	113.48(4)
C(6)-N(1)-H(1)	111.9(7)
S(2)-N(1)-H(1)	110.6(7)
O(2)-S(2)-O(1)	119.64(3)
O(2)-S(2)-O(3)	105.92(3)
O(1)-S(2)-O(3)	107.51(3)
O(2)-S(2)-N(1)	109.56(3)
O(1)-S(2)-N(1)	108.06(3)
O(3)-S(2)-N(1)	105.22(3)
C(4)-O(3)-S(2)	113.95(4)
O(3)-C(4)-C(5)	110.69(5)
O(3)-C(4)-H(4A)	109.5
C(5)-C(4)-H(4A)	109.5
O(3)-C(4)-H(4B)	109.5
C(5)-C(4)-H(4B)	109.5

H(4A)-C(4)-H(4B)	108.1
C(4)-C(5)-C(9)	111.89(5)
C(4)-C(5)-C(6)	109.26(5)
C(9)-C(5)-C(6)	112.95(5)
C(4)-C(5)-H(5)	107.5
C(9)-C(5)-H(5)	107.5
C(6)-C(5)-H(5)	107.5
N(1)-C(6)-C(7)	111.16(3)
N(1)-C(6)-C(5)	110.99(4)
C(7)-C(6)-C(5)	111.66(3)
N(1)-C(6)-H(6)	107.6
C(7)-C(6)-H(6)	107.6
C(5)-C(6)-H(6)	107.6
C(8)-C(7)-C(6)	126.59(4)
C(8)-C(7)-H(7)	116.7
C(6)-C(7)-H(7)	116.7
C(7)-C(8)-H(8A)	120.0
C(7)-C(8)-H(8B)	120.0
H(8A)-C(8)-H(8B)	120.0
C(5)-C(9)-H(9A)	109.5
C(5)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(5)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 3. Torsion angles [°] for 4216.

C(6)-N(1)-S(2)-O(2)	166.00(4)
C(6)-N(1)-S(2)-O(1)	-62.10(5)
C(6)-N(1)-S(2)-O(3)	52.53(5)
O(2)-S(2)-O(3)-C(4)	-170.15(5)
O(1)-S(2)-O(3)-C(4)	60.86(5)
N(1)-S(2)-O(3)-C(4)	-54.15(5)
S(2)-O(3)-C(4)-C(5)	60.71(6)
O(3)-C(4)-C(5)-C(9)	66.17(7)
O(3)-C(4)-C(5)-C(6)	-59.67(7)
S(2)-N(1)-C(6)-C(7)	177.90(2)
S(2)-N(1)-C(6)-C(5)	-57.17(5)
C(4)-C(5)-C(6)-N(1)	58.50(6)
C(9)-C(5)-C(6)-N(1)	-66.73(6)
C(4)-C(5)-C(6)-C(7)	-176.86(4)
C(9)-C(5)-C(6)-C(7)	57.92(5)
N(1)-C(6)-C(7)-C(8)	2.02(5)
C(5)-C(6)-C(7)-C(8)	-122.53(6)

Symmetry transformations used to generate equivalent atoms:

Table 4. Hydrogen bonds for 4216 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(1)#1	0.886(11)	2.092(11)	2.9440(8)	160.9(10)

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,y+1/2,-z+1/2

Appendix C: Published paper

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COMMUNICATION

Gold(I)-catalysed synthesis of cyclic sulfamidates by intramolecular allene hydroamination†

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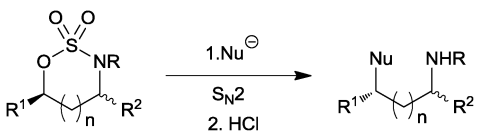
Six-membered cyclic sulfamidates are prepared in high yields by treatment of allenic sulfamates with readily available gold(I) complexes. The reaction enables formation of *N*-substituted quaternary centres and complements existing processes for sulfamidate formation.

Cyclic sulfamidates are versatile intermediates for the synthesis of substituted amines including amino alcohols.[1] They undergo S_N2 reaction at the oxygen-bearing carbon with a variety of nucleophiles (Scheme 1).

Traditionally they are prepared from the corresponding amino alcohols *via* formation of the sulfamidite with thionyl chloride and subsequent Ru-catalysed oxidation (Scheme 2, A).[1]

In recent years, a number of procedures have emerged for the preparation of this useful class of compounds *via* catalytic C–N bond formation.[2] This area has to-date been dominated by metal-catalysed generation of a nitrenoid from a linear sulfamate precursor under oxidising conditions (Scheme 2, B). Subsequent aziridination or C–H bond insertion leads to a range of substitution patterns.

Transition-metal catalysed hydroamination is an increasingly useful method for the preparation of amines,[3] but to our knowledge has not been explored using unsaturated sulfamates as cyclisation precursors. Given the high reactivity of allenes and the use of gold complexes to promote hydroamination with unsaturated tosyl sulfonamides,[4] we decided to investigate the viability of gold-catalysed sulfamidate synthesis using allenic sulfamates (Scheme 2, C).



Scheme 1 Reactivity of cyclic sulfamidates.

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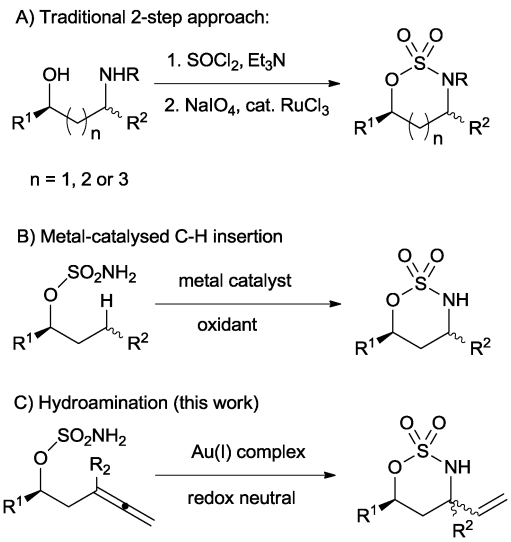
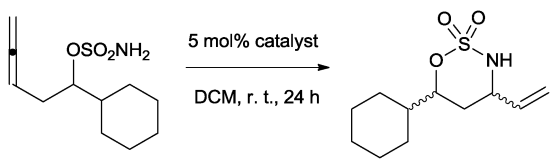
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra for sulfamidate products with characterisation data. CCDC 871548. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc33711h



Scheme 2 Synthetic approaches to sulfamidates.

Our initial test substrate **1** (Table 1) was prepared in three steps from cyclohexane carbaldehyde.[5] To our delight, treatment of **1** with commercially available PPh_3AuNTf_2 (Gagosz's complex)[6] or $PPh_3AuCl/AgOTf$[7] at room temperature in dichloromethane led to the clean formation of sulfamidate **2** (entries 4 and 5). Use of other ligands and counterions on gold (entries 6–8) gave

Table 1 Initial experiments and controls

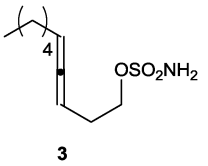
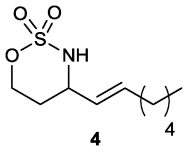
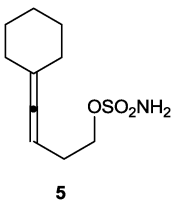
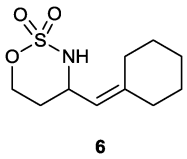
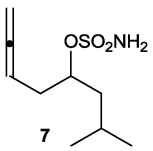
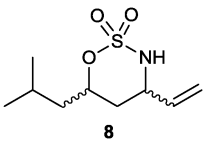
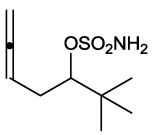
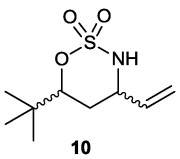
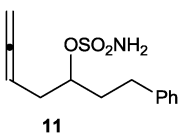
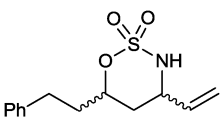
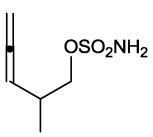
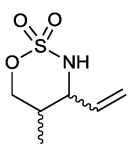


1 **2**

Entry	Catalyst	Yield **2**/%[a]	dr *cis* : *trans*
1	None	0	NA
2	AgOTf	0	NA
3	TfOH	0	NA
4	$(Ph_3P)AuCl/AgOTf$	74	1.7 : 1
5	$(Ph_3P)AuNTf_2$	99	1.2 : 1
6	IPrAuCl/AgOTf	48	1 : 1
7	(2,4-Di-*t*BuPhO)$_3$PAuCl/AgOTf	43	2 : 1
8	(2,4-Di-*t*BuPhO)$_3$PAuCl/$AgNTf_2$	82	1 : 1

[a] Reactions conducted on a 50 mg scale.

Table 2 Substrate scope

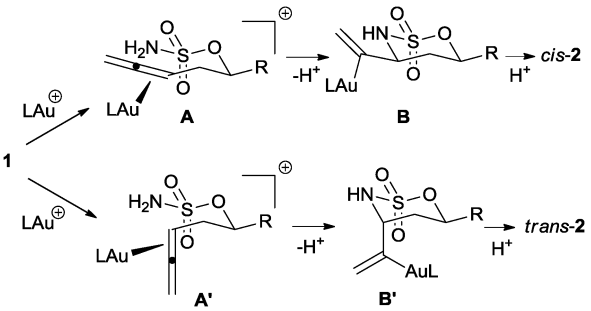
Entry	Sulfamate	Products[a]	Yield (%)
1	 **3**	 **4**	94%
2	 **5**	 **6**	66%
3	 **7**	 **8**	95%[b] (*cis*/*trans* dr 1.8 : 1)
4	 **9**	 **10**	93%[b] (2 : 1)
5	 **11**	 **12**	95% (1.8 : 1)
6	 **13**	 **14**	75% (3 : 1)[c]

[a] 5 mol% $Ph_3PAuNTf_2$, DCM, r.t. 24-120 h, see ESI. [b] Solvent: DCE, temperature 40 °C. [c] Relative stereochemistry not determined.

better diastereoselectivity in some cases, but with diminished yield (See supporting information). Control experiments without any catalyst, with AgOTf only and with TfOH confirmed that the gold complex was necessary for reaction to occur (entries 1–3).

We then prepared a range of substituted substrates designed to demonstrate the scope of the reaction using Gagosz's complex, which had given us the highest yield of **2**, as catalyst (Table 2).[8] Sulfamidate **4** was formed as exclusively the *E*-alkene (Entry 1) in excellent yield. Sulfamate **5**, leading to the formation of sulfamidate **6** containing a trisubstituted olefin, was also a viable substrate under these conditions. Sulfamates **7**, **9** and **11**, derived from secondary alcohols, gave mixtures of 1,3-*cis* and *trans* isomers.

In the case of sulfamidate **2** the diastereomers were separable and the major product was shown to be the 1,3-*cis* isomer (*cis*-**2**) by a single crystal X-ray diffraction study (see ESI†);‡ the other 1,3-disubstituted products were assigned by analogy.[9] The 2-substituted product **14** was formed as a 3 : 1 mixture of diastereomers.



Scheme 3 Possible stereochemical rationale.

Notably, these examples are complementary to the product distribution arising from the Rh-nitrene chemistry of sulfamates, where insertion into tertiary C–H bonds is faster than that into allylic and benzylic C–H bonds, and aziridination often predominates over allylic C–H insertion.[10]

A control experiment, performed by subjecting the separable diastereomer *cis*-**2** to the original reaction conditions, showed that no equilibrium existed between the diastereomers. This is consistent with a kinetically-controlled cyclisation, which is common in other gold-catalysed hydroaminations.[3]

Mechanistically, we anticipate that the reaction occurs *via* an outer sphere mechanism[11] (Scheme 3) leading to *anti* amino-auration of the allene. The *cis* and *trans* diastereomeric products may arise from the conformations A and A′ indicated.

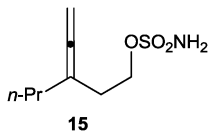
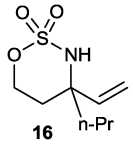
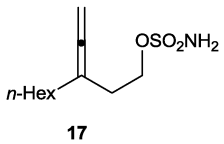
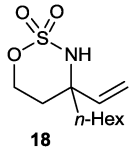
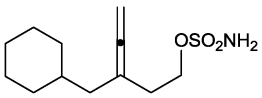
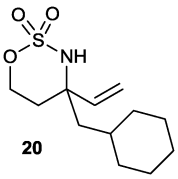
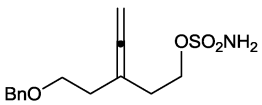
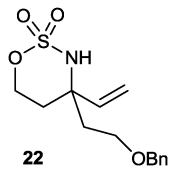
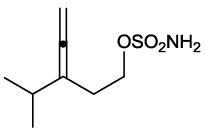
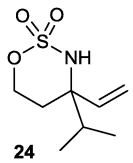
Protonation of the vinyl gold intermediates B and B′ would then give the observed products and regenerate the catalyst. Addition of protic additives (H_2O, AcOH, TfOH) to the reaction mixture did not accelerate the reaction to a measurable extent, suggesting that the final protonation is not the rate-determining step of this process.

The diastereoselectivity observed in the formation of **2**, **8**, **10** and **12** is lower than that normally found in related cyclisations.[12] The explanation for this is currently unclear. At present, we postulate that A and A′ (Scheme 3) are in equilibrium[13] and that the observed diastereoselectivity for the *cis* products is due to faster and irreversible cyclisation of A, which has both the substituent R and the allene in equatorial positions. This would compare favourably with cyclisation of A′, where the allene is in the axial position. However, further studies will be required to establish a well-defined stereochemical model in these systems.

We next decided to determine whether the reaction was suitable for the formation of *N*-substituted quaternary centres (Table 3, overleaf), since this is very rare for catalytic hydroaminations.[14] Gratifyingly, cyclisation of sulfamates **15**, **17**, **19** and **21** occurred cleanly to give the respective products **16**, **18**, **20** and **22** (Entries 1–4). The current limit of the method was reached in the case of substrate **23**, which gave only a trace (~3%) of product **24** after 5 days at 40 °C (Entry 5). Such unsaturated amine derivatives are difficult to access by other methods[15] and have considerable potential for further functionalisation. A general catalytic asymmetric approach to C-tertiary amines has so far proved elusive.[15] Given our results, this new hydroamination reaction has the potential to address this important problem.[16,17]

In summary, we have demonstrated the first gold-catalysed preparation of cyclic sulfamidates, leading to a range of substituted and sterically hindered products under mild conditions.

Table 3 Formation of *N*-substituted quaternary centres

Entry	Sulfamate	Product[a]	Yield (%)
1	 **15**	 **16**	92%
2	 **17**	 **18**	68%
3	 **19**	 **20**	37%
4	 **21**	 **22**	90%
5	 **23**	 **24**	Trace[b]

[a] 5 mol% $Ph_3PAuNTf_2$, DCM, r.t. 24–120 h, see ESI. [b] ~3% of 90% pure product isolated.

Further studies on the scope and limitations of this reaction will be reported in due course. Development of an asymmetric version of this process and other metal-catalysed reactions of sulfamates are also underway in our laboratories.

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Notes and references

‡ X-ray crystallographic data for *cis*-**2** (CCDC 871548): $C_{11}H_{19}NO_3S$, M = 245.33, monoclinic, a = 19.8419(15), b = 5.3049(4), c = 11.5941(9), β = 90.646(4), V = 1220.31(16) Å^3, T = 100(2)K, space group $P2_1/c$, Z = 4, Mo-Kα radiation (λ = 0.71073 Å), GOF = 1.049, agreement index R_1 = 0.0329, 27 110 reflections measured, 4215 unique(R_{int} = 0.0325) which were used in all calculations. The final ωR(F^2) was 0.890.

1 For a recent review, see J. F. Bower, J. Rujirawanich and T. Gallagher, *Org. Biomol. Chem.*, 2010, **8**, 1505.

2 For a review of C–H amination, see D. N. Zalatan and J. Du Bois, *Top. Curr. Chem.*, 2010, **292**, 347.

3 For a review of hydrofunctionalisation of multiple bonds, see (*a*) A. S. K. Hashmi and M. Buehrle, *Aldrichim. Acta*, 2010, **43**, 27; for reviews of nucleophilic cyclisation of allenes, see (*b*) N. Nishina and Y. Yamamoto, *Tetrahedron*, 2009, **65**, 1799 and (*c*) N. Krause and C. Winter, *Chem. Rev.*, 2011, **111**, 1994; for a review of gold-catalysed hydroamination, see (*d*) R. A. Widenhoefer and X. Han, *Eur. J. Org. Chem.*, 2006, **20**, 4555. For a relevant example, see (*e*) N. T. Patil, L. M. Lutete, N. Nishina and Y. Yamamoto, *Tetrahedron Lett.*, 2006, **47**, 4749.

4 The Rh-nitrene chemistry of such compounds has been investigated and products arising from formation of a metal-stabilised 2-aminoallyl intermediate predominate, in contrast to our work. See G. C. Feast, L. W. Page and J. Robertson, *Chem. Commun.*, 2010, **46**, 2835.

5 Allenic alcohols were prepared either by Johnson-Claisen rearrangements of the corresponding propargyl alcohols, see (*a*) S. Ma and W. Gao, *J. Org. Chem.*, 2002, **67**, 6104 or alternatively by Crabbé homologation of homopropargyl alcohols see (*b*) B. M. Trost, A. B. Pinkerton and M. Seidel, *J. Am. Chem. Soc.*, 2001, **123**, 12466. Sulfamate formation was conducted according to standard procedures, see (*c*) C. G. Espino, P. M. Wehn, J. Chow and J. Du Bois, *J. Am. Chem. Soc.*, 2001, **123**, 6935.

6 N. Mézailles, L. Ricard and F. Gagosz, *Org. Lett.*, 2005, **7**, 4133.

7 A. S. K. Hashmi, *Gold Bull.*, 2004, **37**, 51.

8 Reaction times were between 24–120 h, see supporting information.

9 The ^{1}H NMR signals in the olefinic region of the spectra differ consistently for the *cis* and *trans* 1,3-isomers; see ESI† for details.

10 For lead references and mechanistic studies, see (*a*) K. Williams Fiori, C. G. Espino, B. H. Brodsky and J. Du Bois, *Tetrahedron*, 2009, **65**, 3042. For recent work targeted at allylic C–H nitrene insertion using sulfamidates, see (*b*) E. Milczek, N. Boudet and S. Blakey, *Angew. Chem., Int. Ed.*, 2008, **47**, 6825; (*c*) M. E. Harvey, D. G. Musaev and J. Du Bois, *J. Am. Chem. Soc.*, 2011, **133**, 17207 (Ru catalysis) and (*d*) S. M. Paradine and M. C. White, *J. Am. Chem. Soc.*, 2012, **134**, 2036 (Fe catalysis). Notably, there are no examples of insertion into tertiary allylic C–H bonds in these reports.

11 For mechanistic studies, see (*a*) Z. Zhang, C. Liu, R. E. Kinder, X. Han, H. Qian and R. A. Widenhoefer, *J. Am. Chem. Soc.*, 2006, **128**, 9066; (*b*) Z. Zhang and R. A. Widenhoefer, *Org. Lett.*, 2008, **10**, 2079; (*c*) J. J. Kennedy-Smith, S. T. Staben and F. D. Toste, *J. Am. Chem. Soc.*, 2004, **126**, 4526; (*d*) J. Zhang, C.-G. Yang and C. He, *J. Am. Chem. Soc.*, 2006, **128**, 1798; (*e*) A. S. K. Hashmi, J. P. Weyrauch, W. Frey and J. W. Bats, *Org. Lett.*, 2004, **6**, 4391; (*f*) Y. Liu, F. Song, Z. Song, M. Liu and B. Yan, *Org. Lett.*, 2005, **7**, 5409.

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